Bibliographic Data

Application No: 18/408,486

Foreign Priority claimed: ○ Yes ◉ No

35 USC 119 (a-d) conditions met: ☐ Yes ☐ No ☐ Met After Allowance

Verified and Acknowledged: /MANAHIL MIRGHANI ALI ABDALHAMEED/ Examiner's Signature | Initials

Title: METHODS OF USE OF EMULSION FORMULATIONS OF AN NK-1 RECEPTOR ANTAGONIST

FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
01/09/2024	707	1622	092459-0422/8032.US05
RULE			

APPLICANTS

Heron Therapeutics, Inc., San Diego, CA, UNITED STATES

INVENTORS

Thomas B. Ottoboni, Belmont, CA, UNITED STATES

Han Han, Sunnyvale, CA, UNITED STATES

CONTINUING DATA

This application is a CON of 18535853 12/11/2023

18535853 is a CON of 17180593 02/19/2021 PAT 11878074

17180593 is a CON of 16820311 03/16/2020 PAT 11173118

16820311 is a CON of 15965638 04/27/2018 PAT 10624850

15965638 is a CON of 15012532 02/01/2016 PAT 9974742

FOREIGN APPLICATIONS

IF REQUIRED, FOREIGN LICENSE GRANTED**

01/23/2024

**** SMALL ENTITY ****

STATE OR COUNTRY

UNITED STATES

ADDRESS

McDermott Will & Emery LLP
500 North Capitol Street NW
Washington, DC 20001-1531
UNITED STATES

FILING FEE RECEIVED

Bibliographic Data

Application No: 18/408,486

Foreign Priority claimed: ○ Yes ◉ No

35 USC 119 (a-d) conditions met: ☐ Yes ☐ No ☐ Met After Allowance

Verified and Acknowledged: /MANAHIL MIRGHANI ALI ABDALHAMEED/ Examiner's Signature | Initials

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STATE OR COUNTRY

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ADDRESS

McDermott Will & Emery LLP
500 North Capitol Street NW
Washington, DC 20001-1531
UNITED STATES

FILING FEE RECEIVED

$2,800

$2,800

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/408,486	01/09/2024 08:37:20 PM Z ET	092459-0422/8032.US05

Title of Invention

METHODS OF USE OF EMULSION FORMULATIONS OF AN NK-1 RECEPTOR ANTAGONIST

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	5991	FILED BY	Judy Steinkraus
PATENT CENTER #	63894091	AUTHORIZED BY	Peter Brunovskis
CUSTOMER #	108547	FILING DATE	-
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Thomas B. Ottoboni

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
DA / 500417	E202419K39588020	Judy Steinkraus

PRE-AUTHORIZED ACCOUNT

500417

PRE-AUTHORIZED CATEGORY

37 CFR 1.16 (National application filing, search, and examination fees); 37 CFR 1.17 (Patent application and reexamination processing fees); 37 CFR 1.19 (Document supply fees); 37 CFR 1.21 (Miscellaneous fees and charges)

FEE CODE	DESCRIPTION	ITEM PRICE($)	QUANTITY	ITEM TOTAL($)
2830	PROCESSING FEE, EXCEPT IN PROVISIONAL APPLICATIONS	56.00	1	56.00
2817	REQUEST FOR PRIORITIZED EXAMINATION	1680.00	1	1680.00
2111	UTILITY PATENT APPL. SEARCH FEE	280.00	1	280.00
4011	BASIC FILING FEE- UTILITY	64.00	1	64.00

2311	EXAMINATION OF ORIGINAL PATENT APPLICATION	320.00	1	320.00
2202	EACH CLAIM IN EXCESS OF 20	40.00	10	400.00
			TOTAL AMOUNT:	**$2,800.00**

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/408,486	**01/09/2024 08:37:20 PM Z ET**	**092459-0422/8032.US05**

Title of Invention

METHODS OF USE OF EMULSION FORMULATIONS OF AN NK-1 RECEPTOR ANTAGONIST

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	5991	FILED BY	Judy Steinkraus
PATENT CENTER #	63894091	FILING DATE	-
CUSTOMER #	108547	FIRST NAMED INVENTOR	Thomas B. Ottoboni
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Peter Brunovskis

Documents

TOTAL DOCUMENTS: 9

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
ADSaia0014-ADS_jls.pdf	9	Application Data Sheet	2174 KB
Track-1_11-23_aia0424.pdf	1	Track One Request	167 KB
Application_Transmittal_Nonprov.pdf	2	Transmittal of New Application	535 KB
Parent_Signed_Declarations.pdf	2	Oath or Declaration filed	180 KB
New_POA_to_File.pdf	1	Power of Attorney	105 KB
373c_thru_2024_aia0096.pdf	6	Power of Attorney	328 KB

Drawings_mdr.pdf	4	Drawings-only black and white line drawings	966 KB
0422_8032-US05_Specification-APP.TEXT.docx	46	Application body structured text document	110 KB

Warning: All artifacts (SmartArt, Drawings, Charts, etc) have been replaced with images. Bookmarks were found and have been removed. Images have been detected in the abstract section. Please review. You may be missing a drawing heading. At least one claim appears to not end with a period. Please review and revise if necessary.

0422_8032-US05_Specification_.pdf	46	Auxiliary PDF of Application	279 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
ADSaia0014-ADS_jls.pdf	27C2A021D9F4A91E52AF449D067FA6756B2654B41F57D21A2945CEABA9B93EBBFA1686DCC2F1D105BF2BE5CB74CB58E105661FD083F5B287BF06CEFAD7B98912
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Drawings_mdr.pdf	FFC602E20D0BC8D538832BBBD64B42250900A84262142AE3235F19EDC642ACA02BCB1831DB96FB66048DEC2DDC83E665677C6B67171CF22DC424C7EC2C9BFBD0
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0422_8032-US05_Specification_.pdf	734382E43C01BF912FFC12CD2850A3848CBBE2CE8EDB31FD6EA95CF3ADADAB24B20BFAEC5DF5F51188BCDD63CC10BA5124438316388E048AD19FAC9F6932B743

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New International Application Filed with the USPTO as a Receiving Office

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DocCode - SCORE

SCORE Placeholder Sheet for IFW Content

Application Number: 18408486 Document Date: 01/09/2024

The presence of this form in the IFW record indicates that the following document type was received in electronic format on the date identified above. This content is stored in the SCORE database.

Since this was an electronic submission, there is no physical artifact folder, no artifact folder is recorded in PALM, and no paper documents or physical media exist. The TIFF images in the IFW record were created from the original documents that are stored in SCORE.

- Drawing

At the time of document entry (noted above):

- USPTO employees may access SCORE content via DAV or via the SCORE web page.
- External customers may access SCORE content via PAIR using the Supplemental Content tab.

Form Revision Date: March 1, 2019

Doc Code: TRACK1.REQ
Document Description: TrackOne Request

PTO/AIA/424 (11-23)

CERTIFICATION AND REQUEST FOR PRIORITIZED EXAMINATION UNDER 37 CFR 1.102(e) (Page 1 of 1)

First Named Inventor:	Thomas B. Ottoboni	Nonprovisional Application Number (if known):	To be assigned
Title of Invention:	METHODS OF USE OF EMULSION FORMULATIONS OF AN NK-1 RECEPTOR ANTAGONIST		

APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS PRIORITIZED EXAMINATION FOR THE ABOVE-IDENTIFIED APPLICATION.

1. The processing fee set forth in 37 CFR 1.17(i)(1) and the prioritized examination fee set forth in 37 CFR 1.17(c) have been filed with the request. The publication fee requirement is met because that fee, set forth in 37 CFR 1.18(d), is currently $0. The basic filing fee, search fee, and examination fee are filed with the request or have been already been paid. I understand that any required excess claims fees or application size fee must be paid for the application.

2. I understand that the application may not contain, or be amended to contain, more than four independent claims, more than thirty total claims, or any multiple dependent claims, and that any request for an extension of time will cause an outstanding Track I request to be dismissed.

3. The applicable box is checked below:

I. ☑ Original Application (Track One) - Prioritized Examination under § 1.102(e)(1)

i. (a) The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a). This certification and request is being filed with the utility application via USPTO patent electronic filing system.

---OR---

(b) The application is an original nonprovisional plant application filed under 35 U.S.C. 111(a). This certification and request is being filed with the plant application in paper.

ii. An executed inventor's oath or declaration under 37 CFR 1.63 or 37 CFR 1.64 for each inventor, **or** the application data sheet meeting the conditions specified in 37 CFR 1.53(f)(3)(i) is filed with the application.

II. ☐ Request for Continued Examination - Prioritized Examination under § 1.102(e)(2)

i. A request for continued examination has been filed with, or prior to, this form.
ii. If the application is a utility application, this certification and request is being filed via USPTO patent electronic filing system.
iii. The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a), or is a national stage entry under 35 U.S.C. 371.
iv. This certification and request is being filed prior to the mailing of a first Office action responsive to the request for continued examination.
v. No prior request for continued examination has been granted prioritized examination status under 37 CFR 1.102(e)(2).

Signature /Peter Brunovskis/	Date 2024-01-09
Name (Print/Typed) Peter Brunovskis	Practitioner Registration Number 52441

Note: *This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. Submit multiple forms if more than one signature is required.**

☑ *Total of 1 forms are submitted.

PTO/AIA/14 (01-22)
Approved for use through 05/31/2024. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	092459-0422/8032.US05
	Application Number	
Title of Invention	METHODS OF USE OF EMULSION FORMULATIONS OF AN NK-1 RECEPTOR ANTAGONIST	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2:

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Thomas	B.	Ottoboni	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Belmont	State/Province	CA	Country of Residence	US

Mailing Address of Inventor:

Address 1	1211 North Road
Address 2	

City	Belmont	State/Province	CA
Postal Code	94002	Country	US

Inventor 2 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Han		Han	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Sunnyvale	State/Province	CA	Country of Residence	US

Mailing Address of Inventor:

Address 1	820 Lakeknoll Drive
Address 2	

City	Sunnyvale	State/Province	CA
Postal Code	94089	Country	US

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

PTO/AIA/14 (01-22)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	092459-0422/8032.US05
	Application Number	
Title of Invention	METHODS OF USE OF EMULSION FORMULATIONS OF AN NK-1 RECEPTOR ANTAGONIST	

☐ An Address is being provided for the correspondence Information of this application.			
Customer Number	108547		
Email Address		Add Email	Remove Email

Application Information:

Title of the Invention	METHODS OF USE OF EMULSION FORMULATIONS OF AN NK-1 RECEPTOR ANTAGONIST		
Attorney Docket Number	092459-0422/8032.US05	**Small Entity Status Claimed**	☒
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	4	**Suggested Figure for Publication (if any)**	

Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	◉ Customer Number	○ US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	108547		

PTO/AIA/14 (01-22)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	092459-0422/8032.US05
	Application Number	
Title of Invention	METHODS OF USE OF EMULSION FORMULATIONS OF AN NK-1 RECEPTOR ANTAGONIST	

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.
When referring to the current application, please leave the "Application Number" field blank.

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
	Continuation of	18/535853	2023-12-11
Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
18/535853	Continuation of	17/180593	2021-02-19

Prior Application Status	Patented				Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
17/180593	Continuation of	16/820311	2020-03-16	11173118	2021-11-16
Prior Application Status	Patented				Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
16/820311	Continuation of	15/965638	2018-04-27	10624850	2020-04-21
Prior Application Status	Patented				Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
15/965638	Continuation of	15/012532	2016-02-01	9974742	2018-05-22

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button. Add

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)[i] the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Remove

Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)

PTO/AIA/14 (01-22)
Approved for use through 05/31/2024. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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	Application Number	
Title of Invention	METHODS OF USE OF EMULSION FORMULATIONS OF AN NK-1 RECEPTOR ANTAGONIST	

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button. Add

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

PTO/AIA/14 (01-22)
Approved for use through 05/31/2024. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	092459-0422/8032.US05
	Application Number	
Title of Invention	METHODS OF USE OF EMULSION FORMULATIONS OF AN NK-1 RECEPTOR ANTAGONIST	

Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

A. Priority Document Exchange (PDX) - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

B. Search Results from U.S. Application to EPO - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

☐ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	092459-0422/8032.US05
	Application Number	
Title of Invention	METHODS OF USE OF EMULSION FORMULATIONS OF AN NK-1 RECEPTOR ANTAGONIST	

Applicant Information:

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If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

(●) Assignee	( ) Legal Representative under 35 U.S.C. 117	( ) Joint Inventor
( ) Person to whom the inventor is obligated to assign.	( ) Person who shows sufficient proprietary interest	

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor:

If the Applicant is an Organization check here. [X]

Organization Name	Heron Therapeutics, Inc.		
Mailing Address Information For Applicant:			
Address 1	4242 Campus Point Court, Suite 200		
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City	San Diego	**State/Province**	CA
Country	US	Postal Code	92121
Phone Number		Fax Number	
Email Address			

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Assignee Information including Non-Applicant Assignee Information:

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Assignee 1

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

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This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	/Peter Brunovskis/			Date (YYYY-MM-DD)	2024-01-09
First Name	Peter	Last Name	Brunovskis	Registration Number	52441

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Title of Invention	METHODS OF USE OF EMULSION FORMULATIONS OF AN NK-1 RECEPTOR ANTAGONIST	

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

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UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Attorney Docket No.	092459-0422/8032.US05
First Named Inventor	Thomas B. OTTOBONI
Title	METHODS OF USE OF EMULSION FORMULATIONS OF AN NK-1 RECEPTOR ANT
Priority Mail Express® Label No.	Via Patent Center

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

1. ☐ **Fee Transmittal Form** (PTO/SB/17 or equivalent)
2. ☑ **Applicant asserts small entity status.** See 37 CFR 1.27
3. ☐ **Applicant certifies micro entity status.** See 37 CFR 1.29. Applicant must attach form PTO/SB/15A or B or equivalent.
4. ☑ **Specification** [*Total Pages* 46] Both the claims and abstract must start on a new page. *(See MPEP § 608.01(a) for information on the preferred arrangement)*
5. ☑ **Drawing(s)** (35 U.S.C. 113) [*Total Sheets* 4]
6. **Inventor's Oath or Declaration** [*Total Pages* 2] *(including substitute statements under 37 CFR 1.64 and assignments serving as an oath or declaration under 37 CFR 1.63(e))*
   a. ☐ Newly executed (original or copy)
   b. ☑ A copy from a prior application (37 CFR 1.63(d))
7. ☑ **Application Data Sheet** ** See note below.* See 37 CFR 1.76 (PTO/AIA/14 or equivalent)
8. **CD-ROM or CD-R** in duplicate, large table, or Computer Program (*Appendix*)
   ☐ Landscape Table on CD
9. **Nucleotide and/or Amino Acid Sequence Submission** (*if applicable, items a. – c. are required*)
   a. ☐ Computer Readable Form (CRF)
   b. ☐ Specification Sequence Listing on:
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ACCOMPANYING APPLICATION PAPERS

10. ☐ **Assignment Papers** (cover sheet & document(s))
    Name of Assignee Heron Therapeutics, Inc.
11. ☑ **37 CFR 3.73(c) Statement** (*when there is an assignee*) ☑ **Power of Attorney**
12. ☐ **English Translation Document** (*if applicable*)
13. ☐ **Information Disclosure Statement** (PTO/SB/08 or PTO-1449)
    ☐ Copies of citations attached
14. ☐ **Preliminary Amendment**
15. ☐ **Return Receipt Postcard** (*MPEP § 503*) (*Should be specifically itemized*)
16. ☐ **Certified Copy of Priority Document(s)** (*if foreign priority is claimed*)
17. ☐ **Nonpublication Request** Under 35 U.S.C. 122(b)(2)(B)(i). Applicant must attach form PTO/SB/35 or equivalent.
18. ☑ **Other:** Track 1 Request

***Note**: (1) Benefit claims under 37 CFR 1.78 and foreign priority claims under 1.55 **must** be included in an Application Data Sheet (ADS).
(2) For applications filed under 35 U.S.C. 111, the application must contain an ADS specifying the applicant if the applicant is an assignee, person to whom the inventor is under an obligation to assign, or person who otherwise shows sufficient proprietary interest in the matter. See 37 CFR 1.46(b).

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Signature	/Peter Brunovskis/	Date	2024-01-09
Name (Print/Type)	Peter Brunovskis	Registration No. (Attorney/Agent)	52441

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METHODS OF USE OF EMULSION FORMULATIONS OF AN NK-1 RECEPTOR ANTAGONIST

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation of U.S. Application No. 18/535,853, filed December 11, 2023, pending, which is a continuation of U.S. Application No. 17/180,593, filed February 19, 2021, now allowed, which is a continuation of U.S. Application No. 16/820,311, filed March 16, 2020, now U.S. Patent No. 11,173,118, which is a continuation of U.S. Application No. 15/965,638, filed April 27, 2018, now U.S. Patent No. 10,624,850, which is a continuation of U.S. Application No. 15/012,532, filed February 1, 2016, now U.S. Patent No. 9,974,742, each of which is incorporated herein in its entirety.

TECHNICAL FIELD

[0002] The disclosure relates generally to emulsion formulations and systems for the intravenous or parenteral administration of an NK-1 receptor antagonist for treatment of emesis. The emulsion formulations are stable for prolonged periods of time. Also described are methods for preparing the stable NK-1 receptor antagonist emulsions and pharmaceutical formulations.

BACKGROUND

[0003] Emesis is a critical problem experienced as a result of anticancer cytotoxic therapy. Up to 80% of patients will experience chemotherapy-induced nausea and vomiting (CINV) without prophylactic therapy (Vieira dos Santos et al., 2012, J Natl Cancer Inst, 104:1280-1292). Navari et al. (1999, N Engl J Med, 340:190-195) showed that neurokinin-1 (NK-1) receptor antagonists improve CINV when used in combination with cisplatin-based chemotherapy. NK-1 receptor antagonists block binding of substance P to the receptor, thereby preventing or limiting induction of vomiting pathways mediated by the NK-1 receptor (Aziz, 2012, Ann Palliat Med, 1:130-136).

[0004] NK-1 receptor antagonists currently approved and marketed include aprepitant and rolapitant HCl, which are both available in oral form. Not surprisingly, oral dosage forms can create a problem for patients suffering from emesis, specifically, for example, on days two and three of chemotherapy. Accordingly, it is desirable to have injectable formulations to simplify treatment for these patients. Described herein are emulsions formulated for administering to a patient by injection. These emulsions are formulated to contain neurokinin-1 receptor antagonists which may be poorly soluble in aqueous solvents or unstable in aqueous-based liquid formulations.

[0005] Liquid formulations containing NK-1 receptor antagonists having poor solubility and/or poor gastrointestinal permeability characteristics can be very challenging to formulate for purposes of long-term storage and for administration. One means of addressing this challenge is to prepare an emulsion which may both allow preparation of an injectable formulation as well as enhance bioavailability of the active agent once administered.

[0006] Intravenous emulsions should have a very small droplet size to circulate in the bloodstream without causing capillary blockage and embolization. These size limits are typified by USP33-NF28 General Chapter <729> for Globule Size Distribution in Lipid Injectable Emulsions, hereinafter referred to as USP <729>, which defines universal limits for (1) mean droplet size not exceeding 500 nm or 0.5 μm and (2) the population of large-diameter fat globules, expressed as the volume-weighted percentage of fat greater than 5 μm (PFAT5) not exceeding 0.05%, irrespective of the final lipid concentration.

[0007] Emulsion formulations must be physically stable. The droplet size limits defined in USP <729> apply throughout the assigned shelf life. All true emulsions are thermodynamically unstable and may over time undergo a range of processes which tend to increase the droplet size. These include direct droplet coalescence, when two droplets collide and form a single new droplet; and aggregation, in which droplets adhere together to form larger masses. Aggregation may in some cases be a precursor of further coalescence into larger droplets. These processes may result in large aggregates rising to the surface of the container, a phenomenon known as 'creaming', and ultimately to free oil being visible on the emulsion surface, known as 'cracking'.

[0008] Emulsion formulations must also be chemically stable. The drug substance may degrade; for example, lipophilic drugs will partition into the oil phase, which will confer some degree of protection, but hydrolytic degradation may still occur at the oil-water interface. Possible chemical degradation within parenteral fat emulsions includes oxidation of unsaturated fatty acid residues present in triglyceride and lecithin, and hydrolysis of phospholipids leading to the formation of free fatty acids (FFA) and lysophospholipids. Such degradants lower pH, which may then promote further degradation. Thus, pH should be controlled during manufacture and parenteral emulsion formulations may include a buffering agent to provide additional control. Any decrease in pH over the assigned shelf-life may be indicative of chemical degradation.

[0009] In the present application, emulsion formulations were prepared and characterized to identify a formulation and process that will allow an NK-1 receptor antagonist compound to be

incorporated into an emulsion for intravenous injection and remain stable during the shelf life of the formulation.

BRIEF SUMMARY

[0010] The following aspects and embodiments thereof described and illustrated below are meant to be exemplary and illustrative, not limiting in scope.

[0011] In one aspect, a pharmaceutical composition suitable for intravenous administration is provided which comprises a stable emulsion comprising an oil phase, wherein the oil phase comprises a neurokinin 1 (NK-1) receptor antagonist, a surfactant and a co-surfactant; and an aqueous phase, wherein the aqueous phase comprises water, a tonicity agent, and a pH modifier.

[0012] In some embodiments, the NK-1 receptor antagonist is selected from the group consisting of aprepitant, rolapitant, netupitant, lanepitant, vestipitant, orvepitant maleate, casopitant, ezlopitant, serlopitant, befetupitant and maropitant, or a pharmaceutically acceptable salt thereof. In other embodiments, the NK-1 receptor antagonist is poorly soluble in water.

[0013] In some embodiments, the NK-1 receptor antagonist is selected from the group consisting of rolapitant, netupitant, casopitant, ezlopitant, vestipitant, serlopitant, maropitant, and orvepitant.

[0014] In some embodiments, the NK-1 receptor antagonist is not aprepitant.

[0015] In some embodiments, the composition is an oil-in-water emulsion comprising an oil wherein the oil is selected from the group consisting of coconut oil, olive oil, soybean oil, safflower oil, triglycerides, octyl and decyl glycerate, ethyl oleate, glyceryl linoleate, ethyl linoleate, glyceryl oleate, cholesteryl oleate/linoleate or a mixture thereof. In other embodiments, the oil is hydrolyzed. In still other embodiments, the oil is structurally modified.

[0016] In some embodiments, the emulsifier comprises a phospholipid. In another embodiment, the emulsifier is selected from the group consisting of egg phospholipids, soy phospholipids, phosphatidylcholines, phosphatidylethanolamines, phosphatidylserines, phosphatidylglycerols, phosphatidylinositols, phosphatidic acids, mixed chain phospholipids, lysophospholipids, hydrogenated phospholipids, partially hydrogenated phospholipids, and mixtures thereof.

[0017] In some embodiments, the co-surfactant comprises an alcohol. In other embodiments, the co-surfactant is ethanol.

[0018] In some embodiments, the pH modifier comprises an oleate or pharmaceutically acceptable salt thereof. In other embodiments, the oleate is sodium, potassium or ammonium oleate. In yet other embodiments, the pH modifier is sodium oleate or a pharmaceutically acceptable salt thereof.

[0019] In some embodiments, the pH modifier comprises a buffer. In other embodiments, the buffer is selected from the group consisting of phosphate buffer, citrate buffer, Tris buffer, carbonate buffer, succinate buffer, maleate buffer and borate buffer. In still other embodiments, the buffer is selected from the group, phosphate buffered saline (PBS), modified PBS (PBS-mod) and citrate buffer.

[0020] In some embodiments, the pH modifier comprises an oleate and a buffer. In other embodiments, the oleate is sodium oleate and the buffer is Tris buffer.

[0021] In some embodiments, the pH modifier is selected from the group consisting of sodium hydroxide, potassium hydroxide, magnesium hydroxide, sodium carbonate, Tris, sodium linoleate, sodium oleate, potassium oleate, ammonium oleate, potassium carbonate, potassium linoleate, and mixtures thereof.

[0022] In some embodiments, the composition comprises about 5 wt/wt% (weight/weight %) to 15 wt/wt%, 5 wt/wt% to 10 wt/wt%, 7 wt/wt% to 10 wt/wt%, 8 wt/wt% to 9 wt/wt%, or 9 wt/wt% to 10 wt/wt% oil. In another embodiment, the composition comprises about 8 wt/wt5, 8.5 wt/wt%, 9 wt/wt%, 9.5 wt/wt%, 10 wt/wt%, or 10.5 wt/wt% oil. In still other embodiments, the oil is soybean oil.

[0023] In some embodiments, the composition comprises about 10 wt/wt% to 20 wt/wt%, 12 wt/wt% to 17 wt/wt%, 13 wt/wt% to 16 wt/wt%, 13 wt/wt% to 15 wt/wt%, 14 wt/wt% to 15 wt/wt%, or 13 wt/wt% to 14 wt/wt% emulsifier. In other embodiments, the composition comprises about 13 wt/wt%, 13.5 wt/wt%, 14 wt/wt%, 14.5 wt/wt%, 15 wt/wt%, 16 wt/wt%, 17 wt/wt%, 18 wt/wt%, 19 wt/wt% or 20 wt/wt% emulsifier. In still other embodiments, the emulsifier is a lecithin. In other embodiments, the lecithin is an egg yolk lecithin.

[0024] In some embodiments, the composition comprises about 0.05 wt/wt% to 1.5 wt/wt%, 0.1 wt/wt% to 1.0 wt/wt%, 0.2 wt/wt% to 0.8 wt/wt%, 0.3 wt/wt% to 0.7 wt/wt%, 0.4 wt/wt% to 0.6 wt/wt%, 0.4 wt/wt% to 0.5 wt/wt% oleate or salt thereof. In other embodiments, the composition comprises about 0.05 wt/wt%, 0.1 wt/wt%, 0.2 wt/wt%, 0.3 wt/wt%, 0.4 wt/wt%, 0.45 wt/wt%, 0.5 wt/wt%, 0.6 wt/wt%, 0.7 wt/wt%, 0.8 wt/wt%, 0.9 wt/wt%, 1.0 wt/wt% or 1.5 wt/wt% oleate or salt thereof. In still other embodiments, the oleate is sodium oleate. In still another embodiment, the oleate or sodium oleate is the pH modifier.

[0025] In some embodiments, the composition comprises about 20 wt/wt% to 50 wt/wt%, 30 wt/wt% to 50 wt/wt%, 35 wt/wt% to 45 wt/wt%, 30 wt/wt% to 45 wt/wt%, 37 wt/wt% to 42 wt/wt%, 38 wt/wt% to 40 wt/wt%, 30 wt/wt%, 31 wt/wt%, 32 wt/wt%, 33 wt/wt%, 34 wt/wt%, 35 wt/wt%,

36 wt/wt%, 37 wt/wt%, 38 wt/wt%, 39 wt/wt%, 40 wt/wt%, 41 wt/wt%, 42 wt/wt%, 43 wt/wt%, 44 wt/wt%, 45 wt/wt%, 46 wt/wt%, 47 wt/wt%, 48 wt/wt%, 49 wt/wt%, 50 wt/wt% of oil expressed as a percentage of the weight of the oil per the sum of weight of oil, emulsifier and oleate in a unit of the composition. In other embodiments, the oil is soybean oil.

[0026] In some embodiments, the composition comprises about 20 wt/wt% to 50 wt/wt%, 30 wt/wt% to 50 wt/wt%, 35 wt/wt% to 45 wt/wt%, 30 wt/wt% to 45 wt/wt%, 37 wt/wt% to 42 wt/wt%, 38 wt/wt% to 40 wt/wt%, 30 wt/wt%, 31 wt/wt%, 32 wt/wt%, 33 wt/wt%, 34 wt/wt%, 35 wt/wt%, 36 wt/wt%, 37 wt/wt%, 38 wt/wt%, 39 wt/wt%, 40 wt/wt%, 41 wt/wt%, 42 wt/wt%, 43 wt/wt%, 44 wt/wt%, 45 wt/wt%, 46 wt/wt%, 47 wt/wt%, 48 wt/wt%, 49 wt/wt%, 50 wt/wt% of oil expressed as a percentage of the weight of the oil per the sum of weight of oil and emulsifier in a unit of the composition. In other embodiments, the oil is soybean oil.

[0027] In some embodiments, the composition comprises about 40 wt/wt% to 80 wt/wt%, 50 wt/wt% to 70 wt/wt%, 55 wt/wt% to 65 wt/wt%, 57 wt/wt% to 63 wt/wt%, 58 to 60 wt/wt%, 35 wt/wt% to 40 wt/wt%, 30 wt/wt% to 40 wt/wt%, 50 wt/wt%, 51 wt/wt%, 52 wt/wt%, 53 wt/wt%, 54 wt/wt%, 55 wt/wt%, 56 wt/wt%, 57 wt/wt%, 58 wt/wt%, 59 wt/wt%, 60 wt/wt%, 61 wt/wt%, 62 wt/wt%, 63 wt/wt%, 64 wt/wt%, 65 wt/wt%, 66 wt/wt%, 67 wt/wt%, 68 wt/wt%, 69 wt/wt%, 70 wt/wt% of emulsifier expressed as a percentage of the weight of emulsifier per the sum of weight of oil, emulsifier and oleate in a unit of the composition. In other embodiments, the emulsifier is a lecithin. In still other embodiments, the lecithin is an egg yolk lecithin.

[0028] In some embodiments, the composition comprises about 40 wt/wt% to 80 wt/wt%, 50 wt/wt% to 70 wt/wt%, 55 wt/wt% to 65 wt/wt%, 57 wt/wt% to 63 wt/wt%, 58 to 60 wt/wt%, 35 wt/wt% to 40 wt/wt%, 30 wt/wt% to 40 wt/wt%, 50 wt/wt%, 51 wt/wt%, 52 wt/wt%, 53 wt/wt%, 54 wt/wt%, 55 wt/wt%, 56 wt/wt%, 57 wt/wt%, 58 wt/wt%, 59 wt/wt%, 60 wt/wt%, 61 wt/wt%, 62 wt/wt%, 63 wt/wt%, 64 wt/wt%, 65 wt/wt%, 66 wt/wt%, 67 wt/wt%, 68 wt/wt%, 69 wt/wt%, 70 wt/wt% of emulsifier expressed as a percentage of the weight of emulsifier per the sum of weight of oil and emulsifier in a unit of the composition. In other embodiments, the emulsifier is a lecithin. In still other embodiments, the lecithin is an egg yolk lecithin.

[0029] In some embodiments, the ratio of oil to NK-1 receptor antagonist (wt%:wt%) in the composition ranges from about 5:1 to 20:1, 5:1 to 15:1, 5:1 to 10:1, 11:1 to 20:1, 11:1 to 15:1, 12:1 to 16:1, 12:1 to 14:1, 11:1 to 15:1, 12:1 to 14:1, 12.5:1 to 13.5:1, 13:1 to 14:1, or 12:1 to 15:1. In other embodiments, the ratio of oil to NK-1 receptor antagonist (wt%:wt%) in the composition is

about 11:1 to 20:1, 11:1 to 15:1, 12:1 to 16:1, 12:1 to 14:1, 5:1, 6:1, 7:1, 8:1, 9:1, 10:1, 11:1, 11.5:1, 12:1, 12.5:1, 13:1, 13.5:1, 14:1, 14.5:1 or 15:1, 15.5:1, 16:1.

[0030] In some embodiments, the ratio of emulsifier to NK-1 receptor antagonist (wt%:wt%) in the composition ranges from about 10:1 to 30:1, 10:1 to 20:1, 15:1 to 30:1, 20:1 to 25:1, 18:1 to 22:1, 19:1 to 20:1, or 10:1 to 30:1. In other embodiments, the ratio of emulsifier:NK-1 receptor antagonist (wt%:wt%) in the composition is about 10:1, 11:1, 13:1, 14:1, 15:1, 18:1, 19:1, 20:1, 21:1, 22:1 23:1, 24:1, 25:1, or 30:1.

[0031] In some embodiments, the ratio of (emulsifier plus oil) to NK-1 receptor antagonist (wt%:wt%) in the composition ranges from about 20:1 to 40:1, 25:1 to 35:1, 30:1 to 35:1, or 32:1 to 34:1. In other embodiments, the ratio of (emulsifier plus oil) to NK-1 receptor antagonist is about 25:1, 26:1, 27:1, 28:1, 29:1 30:1, 31:1, 32:1, 33:1, 34:1, 35:1, 36:1, 37:1, 38:1 or 40:1.

[0032] In some embodiments, the ratio of emulsifier to oil (wt%:wt%) in the composition ranges from about 0.5:1, to 4:1, 1:1 to 2:1, 1.25:1 to 1.75:1, or 1.4:1 to 1.6:1. In other embodiments, the ratio of emulsifier to oil (wt%:wt%) in the composition is about 0.5:1, 0.5:1, 0.6:1, 0.7:1, 0.8:1, 0.9:1, 1:1, 1.1:1, 1.2:1, 1.3:1, 1.4:1, 1.5:1, 1.6:1, 1.7:1, 1.8:1, 1.9:1, 2:1, 1.05:1, 1.15:1, 1.25:1, 1.35:1, 1.45:1, 1.55:1, 1.65:1, 1.75:1, 1.85:1, or 1.95:1.

[0033] In some embodiments, a therapeutic dose of the pharmaceutical composition comprises about 1 to 4 g, 1.5 to 3 g, 1.8 to 2.8 g, 2.3 to 2.8 g, 1.8 to 2.3 g, 1 g, 1.1 g, 1.2 g, 1.3 g, 1.4 g, 1.5 g, 1.6 g, 1.7 g, 1.8 g. 1.9 g, 2 g, 2.1 g, 2.2 g, 2.3 g, 2.4 g, 2.5 g, 2.6 g, 2.7 g, 2.8 g. 2.9 g, 3 g, 3.1 g, 3.2 g, 3.3 g, 3.4 g, 3.5 g, 3.6 g, 3.7 g, 3.8 g. 3.9 g, 4 g emulsifier. In other embodiments, the emulsifier is a lecithin. In still other embodiments, the emulsifier is egg yolk lecithin.

[0034] In some embodiments, a therapeutic dose of the pharmaceutical composition comprises about 0.5 to 3 g, 1 to 2.5 g, 1 to 2 g, 1 to 1.5 g, 1.5 g to 2 g, 0.5g 0.6 g, 0.7 g, 0.8 g, 0.9 g, 1 g, 1.1 g, 1.2 g, 1.3 g, 1.4 g, 1.5 g, 1.6 g, 1.7 g, 1.8 g. 1.9 g, 2 g, 2.1 g, 2.2 g, 2.3 g, 2.4 g, 2.5 g oil. In other embodiments, the oil is soybean oil.

[0035] In some embodiments, a therapeutic dose of the pharmaceutical composition comprises about 50 to 600 mg, 100 to 600 mg, 100 to 500 mg, 100 to 400 mg, 100 to 300 mg, 100 to 200 mg, 200 to 400 mg, 50 to 250 mg, 75 to 200 mg, 100 to 150 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 160 mg, 170 mg, 180 mg, 190 mg, 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, or 600 mg of the NK-1 receptor antagonist.

[0036] In some embodiments, the composition comprises about 0 wt/wt% to 10 wt/wt%, 1 wt/wt% to 9 wt/wt%, 2 wt/wt% to 6 wt/wt%, 2 wt/wt% to 4 wt/wt% or 2 wt/wt% to 3 wt/wt% co-surfactant.

In other embodiments, the composition comprises less than 10 wt/wt%, less than 9 wt/wt%, less than 8 wt/wt%, less than 7, less than 6 wt/wt%, less than 5 wt/wt%, less than 4 wt/wt%, less than 3 wt/wt%, less than 2 wt/wt% or less than 1 wt/wt% co-surfactant.

[0037] In some embodiments, the composition comprises about 0 wt/wt% to 10 wt/wt%, 1 wt/wt% to 9 wt/wt%, or 2 wt/wt% to 6 wt/wt% ethanol. In other embodiments, the composition comprises less than 10 wt/wt%, less than 9 wt/wt%, less than 8 wt/wt%, less than 7, less than 6 wt/wt%, less than 5 wt/wt%, less than 4 wt/wt%, less than 3 wt/wt%, less than 2 wt/wt% or less than 1 wt/wt% ethanol.

[0038] In some embodiments, the aqueous phase of the emulsion comprises a tonicity agent, a pH modifier, and water.

[0039] In some embodiments, the aqueous phase of the emulsion comprises an osmotic agent, a pH modifier, and water.

[0040] In some embodiments, the aqueous phase of the emulsion comprises a tonicity agent, an osmotic agent, a pH modifier, and water.

[0041] In some embodiments, the aqueous phase further comprises a buffer.

[0042] In some embodiments, the aqueous phase comprises a buffer but does not comprise a pH modifier which is different from the buffer. In other embodiments, the buffer functions as both a pH modifier agent and a buffer.

[0043] In some embodiments, when the aqueous phase comprises a buffer, the composition contains no tonicity agent.

[0044] In some embodiments, the buffer is selected from the group consisting of phosphate buffer, citrate buffer, Tris buffer, carbonate buffer, succinate buffer, maleate buffer and borate buffer. In other embodiments, the buffer is selected from the group, phosphate buffered saline (PBS), modified PBS (PBS-mod) and citrate buffer.

[0045] In some embodiments, the aqueous phase comprises a buffer, that when mixed with the oil phase will provide a substantially isotonic oil in water emulsion.

[0046] In some embodiments, the osmotic agent is selected from the group consisting of glycerol, sorbitol, xylitol, mannitol, glucose, trehalose, maltose, sucrose, raffinose, lactose, dextran, polyethylene glycol, or propylene glycol. In other embodiments, the osmotic agent is an inorganic salt such as sodium chloride and mixtures thereof.

[0047] In some embodiments, the composition has a pH of about 6 to 9, 7 to 9, 7.5 to 9, 7.5 to 8.5, 8 to 9, 6 to 8, 7 to 8, or 6, 7, 8 or 9.

[0048] In some embodiments, the composition comprises about 0 wt/wt% to 25 wt/wt%, 2 wt/wt% to 20 wt/wt%, 3 wt/wt% to 15 wt/wt%, or 3 wt/wt% to 8 wt/wt% tonicity agent. In other embodiments, the composition comprises about 1 wt/wt%, 2 wt/wt%, 3 wt/wt%, 4 wt/wt%, 5 wt/wt%, 6 wt/wt%, 7 wt/wt%, 8 wt/wt%, 9 wt/wt%, or 10 wt/wt%, 11 wt/wt%, 12 wt/wt%, 13 wt/wt%, 14 wt/wt%, 15 wt/wt%, 16 wt/wt%, 17 wt/wt%, 18 wt/wt%, 19 wt/wt%, or 20 wt/wt%, 21 wt/wt%, 22 wt/wt%, 23 wt/wt%, 24 wt/wt%, 25 wt/wt% tonicity agent. In still other embodiments, the composition comprises no tonicity agent.

[0049] In some embodiments, the composition comprises about 0 wt/wt% to 25 wt/wt%, 2 wt/wt% to 20 wt/wt%, 3 wt/wt% to 15 wt/wt%, or 3 wt/wt% to 8 wt/wt% osmotic agent. In other embodiments, the composition comprises about 1 wt/wt%, 2 wt/wt%, 3 wt/wt%, 4 wt/wt%, 5 wt/wt%, 6 wt/wt%, 7 wt/wt%, 8 wt/wt%, 9 wt/wt%, or 10 wt/wt%, 11 wt/wt%, 12 wt/wt%, 13 wt/wt%, 14 wt/wt%, 15 wt/wt%, 16 wt/wt%, 17 wt/wt%, 18 wt/wt%, 19 wt/wt%, or 20 wt/wt%, 21 wt/wt%, 22 wt/wt%, 23 wt/wt%, 24 wt/wt%, 25 wt/wt% osmotic agent. In still other embodiments, the composition comprises no osmotic agent.

[0050] In some embodiments, the aqueous phase comprises a dose of dexamethasone sodium phosphate in a therapeutic dose of the pharmaceutical composition. In other embodiments, the dose of dexamethasone sodium phosphate ranges from about 0.5 mg to 30 mg, 0.5 mg to 25 mg, 1 mg to 20 mg, 10 mg to 20 mg, or 3 mg to 16 mg. In still other embodiments, the dose of dexamethasone sodium phosphate is about 9 mg or 16 mg in a therapeutic dose of the pharmaceutical composition. In these embodiments comprising a dose of dexamethasone, the therapeutic dose of the pharmaceutical composition comprises about 50 to 600 mg, 100 to 600 mg, 100 to 500 mg, 100 to 400 mg, 100 to 300 mg, 100 to 200 mg, 200 to 400 mg, 50 to 250 mg, 75 to 200 mg, 100 to 150 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 160 mg, 170 mg, 180 mg, 190 mg, 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, or 600 mg of the NK-1 receptor antagonist.

[0051] In some embodiments, the oil phase comprises a dose of dexamethasone in a therapeutic dose of the pharmaceutical composition. In other embodiments, the dose of dexamethasone ranges from about 0.5 mg to 30 mg, 0.5 mg to 20 mg, 1 mg to 18 mg, 10 mg to 20 mg, or 3 mg to 16 mg. In other embodiments, the dose of dexamethasone is about 8 mg or 12 mg in a therapeutic dose of the pharmaceutical composition. In these embodiments comprising a dose of dexamethasone, the therapeutic dose of the pharmaceutical composition comprises about 50 to 600 mg, 100 to 600 mg, 100 to 500 mg, 100 to 400 mg, 100 to 300 mg, 100 to 200 mg, 200 to 400 mg, 50 to 250 mg, 75 to 200 mg, 100 to 150 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 160 mg, 170 mg, 180

mg, 190 mg, 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, or 600 mg of the NK-1 receptor antagonist

[0052] In some embodiments, the emulsion comprises about 0.002 wt/wt% to 0.2 wt/wt%, 0.003 wt/wt% to 0.16 wt/wt%, 0.02 wt/wt% to 0.1 wt/wt% dexamethasone sodium phosphate.

[0053] In some embodiments, the composition is a stable system maintaining an intensity-weighted mean particle size as determined by dynamic light scattering (DLS) of about 50 nm to 1000 nm, 50 to 500 nm, 50 nm to 400 nm, 50 nm to 300 nm, 50 nm to 200 nm or 50 nm to 100 nm. In another embodiment, the average droplet size is maintained below 500 nm for a period of at least 1 month, 3 months, 6 months, 9 months, 12 months, 2 years or 3 years at room temperature. In other embodiments, the average droplet size is maintained below 500 nm for a period of at least 1 month, 3 months, 6 months, 9 months, 12 months, 2 years or 3 years at 5 °C.

[0054] In another aspect, a method for preparing an emulsion comprising an NK-1 receptor antagonist compound and suitable for parenteral administration is provided.

[0055] In some embodiments, the administration is intravenous administration.

[0056] In some embodiments, the method comprises: a) preparing an oil phase by dissolving the antagonist compound and an emulsifier in ethanol, then adding in oil to generate an oil-based mixture; b) preparing an aqueous phase by mixing water, optionally with a tonicity agent, optionally with an osmotic agent and optionally with a pH modifier and optionally with a buffer to generate an aqueous mixture; c) combining the oil-based mixture and the aqueous mixture and subjecting this to high speed homogenization to generate a crude emulsion; and d) subjecting the crude emulsion to high pressure homogenization to generate a fine emulsion.

[0057] In some embodiments, preparing the oil phase further comprises dissolving dexamethasone with the antagonist compound and the emulsifier in the ethanol.

[0058] In some embodiments, the method comprises: a) combining a NK-1 receptor antagonist, an emulsifier, and an alcohol with an oil to generate an oil phase; (b) combining water, a tonicity agent, a pH modifier, and optionally a buffer to generate an aqueous phase; (c) homogenizing the oil phase with the aqueous phase to generate the pharmaceutical emulsion; and (d) sterilizing the pharmaceutical emulsion. In other embodiments, the homogenizing comprises high speed homogenization.

[0059] In some embodiments, the method comprises: a) preparing an oil phase by dissolving the antagonist compound and an emulsifier in ethanol and oil to generate an oil-based mixture; b) preparing an aqueous phase by mixing water, optionally with a tonicity agent, optionally with an

osmotic agent and optionally with a pH modifier and optionally with a buffer to generate an aqueous mixture; c) combining the oil-based mixture and the aqueous mixture and subjecting this to homogenization to generate a crude emulsion; and d) subjecting the crude emulsion to homogenization to generate a fine emulsion. In other embodiments, the subjecting the homogenization to generate a crude emulsion is high-speed homogenization. In still other embodiments, the homogenization to generate a fine emulsion is a high pressure homogenization.

[0060] In some embodiments, preparing the oil phase further comprises dissolving dexamethasone with the antagonist compound and the emulsifier in the ethanol and oil.

[0061] In some embodiments, preparing the aqueous phase further comprises mixing dexamethasone with the water, tonicity agent, pH modifier, and a buffer. In other embodiments, the dexamethasone is a salt of dexamethasone. In still other embodiments, the dexamethasone is dexamethasone sodium phosphate.

[0062] In some embodiments, the method further comprises sterilizing the fine emulsion to generate the final emulsion, wherein the final emulsion is suitable for injection into a subject.

[0063] In some embodiments, the dissolution in ethanol is performed at a temperature of about 25 °C to 80 °C, 40 °C to 75 °C, 60 °C to 70 °C, or at about 25 °C, 35 °C, 45 °C, 60 °C, 65 °C, 70 °C or 75 °C.

[0064] In some embodiments, the high-speed homogenization is performed at a speed of about 2,000 rpm (revolutions per minute) to 25,000 rpm. In other embodiments, the high-speed homogenization is performed at a speed of about 20,000 rpm. In still other embodiments, the high-speed homogenization is performed at a speed of about 3600 rpm.

[0065] In some embodiments, the high-speed homogenization is performed for a time period of about 0.5 min to 1 hour, 1 min to 45 min, or 1 min to 30 min. In other embodiments, the high-speed homogenization is performed for a time period of about 20 to 40 min or for about 30 min.

[0066] In some embodiments, the high-speed homogenization is performed at about 10 °C to about 60 °C, 20 °C to about 60 °C, about 30 °C to about 50 °C, or about 35 °C to about 45 °C. In another embodiment, the high-speed homogenization is performed at about 25 °C, 30 °C, 35 °C, 40 °C, 45 °C or 50 °C.

[0067] In some embodiments, the high-pressure homogenization is performed at a pressure of about 10,000 psi (pounds per square inch) to 30,000 psi. In other embodiments, the high-pressure homogenization is performed at a pressure of about 20,000 psi.

[0068] In some embodiments, the high-pressure homogenization is performed with cooling. In another embodiment, the high-pressure homogenization is performed with cooling which is sufficient to bring the temperature of the emulsion at the outlet of the process to about 0 °C to about 60 °C, about 10 °C to about 40 °C, about 20 °C to about 30 °C, or to about 20 °C, 25 °C or 30 °C within the time period.

[0069] In some embodiments, the sterilizing the fine emulsion comprises filtering the fine emulsion through a nylon filter. In other embodiments, the nylon filter is a Posidyne® filter. In yet another embodiment, the filter has a pore size of about 0.2 μm (micrometers).

[0070] In another aspect, the compositions described herein are for treatment of a subject, and the composition is administered via injection to a subject in need.

[0071] In some embodiments, the compositions are for use in a method for the treatment of emesis induced by a chemotherapeutic agent, by radiation-induced nausea and vomiting, and/or by post-operative induced nausea and vomiting in a subject. In other embodiments, the treatment comprises administering to the subject a composition comprising an NK-1 receptor antagonist as described herein. In still other embodiments, the compositions are for use in preventing or treating acute and delayed nausea and vomiting.

[0072] Additional embodiments of the present compositions and methods and the like, will be apparent from the following description, drawings, examples, and claims. As can be appreciated from the foregoing and following description, each and every feature described herein, and each and every combination of two or more of such features, is included within the scope of the present disclosure provided that the features included in such a combination are not mutually inconsistent. In addition, any feature or combination of features may be specifically excluded from any embodiment of the present invention. Additional aspects and advantages of the present invention are set forth in the following description and claims, particularly when considered in conjunction with the accompanying examples and drawings.

BRIEF DESCRIPTION OF DRAWINGS

[0073] FIGS. 1A-1D provides microscope images of samples from Examples 1, 2, 3 and 6 after a freeze-thaw cycle. FIG. 1A: Example 1, FIG. 1B: Example 2, FIG. 1C: Example 3, FIG. 1D: Example 6

[0074] FIG. 2 shows plasma levels of aprepitant after injection of a fosaprepitant solution (●) or an aprepitant emulsion prepared as described herein (▲).

[0075] FIG. 3 shows plasma levels of aprepitant after injection of a solution of fosaprepitant (▲) or after injection of an emulsion containing aprepitant and dexamethasone prepared as described herein (●).

[0076] FIG. 4 shows plasma levels of dexamethasone after injection of a solution of dexamethasone sodium phosphate (●) or after injection of an emulsion containing aprepitant and dexamethasone prepared as described herein (▲).

DETAILED DESCRIPTION

[0077] Various aspects now will be described more fully hereinafter. Such aspects may, however, be embodied in many different forms and should not be construed as limited to the embodiments set forth herein; rather, these embodiments are provided so that this disclosure will be thorough and complete, and will fully convey its scope to those skilled in the art.

I. DEFINITIONS

[0078] As used in this specification, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to a "polymer" includes a single polymer as well as two or more of the same or different polymers, reference to an "excipient" includes a single excipient as well as two or more of the same or different excipients, and the like.

[0079] Where a range of values is provided, it is intended that each intervening value between the upper and lower limit of that range and any other stated or intervening value in that stated range is encompassed within the disclosure. For example, if a range of 1 μm to 8 μm is stated, it is intended that 2 μm, 3 μm, 4 μm, 5 μm, 6 μm, and 7 μm are also explicitly disclosed, as well as the range of values greater than or equal to 1 μm and the range of values less than or equal to 8 μm. As used herein, the term "about" means ±5%, ±10%, or ±20% of the value being modified.

[0080] The term "emulsion" or "emulsion formulation" means a colloidal dispersion of two immiscible liquids in the form of droplets, whose diameter, in general, is between 10 nanometers and 100 microns. An emulsion is denoted by the symbol O/W (oil-in-water) if the continuous phase is an aqueous solution and by W/O (water-in-oil) if the continuous phase is an oil. Other examples of emulsions such as O/W/O (oil-in-water-oil) include oil droplets contained within aqueous droplets dispersed in a continuous oil phase.

[0081] "Physically stable" emulsions will meet the criteria under USP <729>, which defines universal limits for (1) mean droplet size not exceeding 500 nm or 0.5 μm and (2) the population of large-diameter fat globules, expressed as the volume-weighted percentage of fat greater than 5 μm

(PFAT5) not exceeding 0.05%, at 5 °C or room temperature for a designated storage time period. In addition, physically stable emulsions will have no visible NK-1 receptor antagonist crystals upon storage at 5 °C or room temperature for a designated time period. Crystals are considered visible when viewed at magnification of 4X to 10X. An emulsion is physically stable if it meets the criteria under USP <729> and NK-1 receptor antagonist crystals are not visible upon storage at 5 °C or room temperature for a time period equal to or at least 1 week, 2 weeks, 4 weeks, 1 month, 2 months, 6 months, 1 year or 2 years.

[0082] "Chemically stable" emulsions of the disclosure are ones in which the concentration of the active component (i.e., the drug being delivered) does not change by more than about 20% under appropriate storage conditions for at least 1 month. In certain embodiments, the concentration the NK-1 receptor antagonist in an emulsion of the present disclosure does not change by more than about 5%, 10%, 15% or 20% under appropriate storage conditions for at least 1, 2, 3, 4, 5, 6, 9, 12, 15, 18, or 24 months.

[0083] In one example, the stable emulsion compositions of the disclosure are stable over a wide range of temperatures, e.g., −20 °C to 40 °C. The compositions of the disclosure may be stored at about 5 °C to about 25 °C.

[0084] "Oil phase" in a water-in-oil emulsion refers to all components in the formulation that individually exceed their solubility limit in the water phase; these are materials that generally have solubilities of less than 1% in distilled water, however, water phase components such as salts may decrease the solubility of certain oils resulting in their partitioning into the oil phase. The oil phase refers to the non-aqueous portion of a water-in-oil emulsion.

[0085] "Aqueous phase" or "water phase" in a water-in-oil emulsion refers to the water present and any components that are water soluble, i.e., have not exceeded their solubility limit in water. "Aqueous phase", as used herein, includes a water-containing liquid which can contain pharmaceutically acceptable additives such as acidifying, alkalizing, buffering, chelating, complexing and solubilizing agents, antioxidants and antimicrobial preservatives, humectants, suspending and/or viscosity modifying agents, tonicity and wetting or other biocompatible materials. The aqueous phase refers to the non-oil portion of a water-in-oil emulsion.

[0086] An "emulsifier" refers to a compound that deters the separation of the injectable emulsion into individual oil and aqueous phases. Emulsifiers useful in the present disclosure generally are (1) compatible with the other ingredients of the stable emulsions of the present disclosure, (2) do not

interfere with the stability or efficacy of the drugs contained in the emulsions, (3) are stable and do not deteriorate in the preparation, and (4) are non-toxic.

[0087] Suitable emulsifiers include, but are not limited to, propylene glycol mono- and di-fatty acid esters, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene fatty acid esters, polyoxyethylene-polyoxypropylene co-polymers and block co-polymers, salts of fatty alcohol sulphates, sorbitan fatty acid esters, esters of polyethylene-glycol glycerol ethers, oil and wax based emulsifiers, glycerol monostearate, glycerine sorbitan fatty acid esters and phospholipids.

[0088] A "phospholipid" refers to a triester of glycerol in which the secondary alcohol and one of the primary alcohols has been esterified with fatty acids and the other primary alcohol has been esterified with a phosphate group. Exemplary phospholipids useful in the present invention include, but are not limited to, phosphatidyl chlorine, lecithin (a mixture of choline ester of phosphorylated diacylglyceride), phosphatidylethanolamine, phosphatidylglycerol, phosphatidic acid with about 4 to about 22 carbon atoms, and more generally from about 10 to about 18 carbon atoms and varying degrees of saturation. The phospholipids can have any combination of fatty acid as its fatty acyl side chain, for example, the phospholipids can have a saturated fatty acid such as a decanoic acid, lauric acid, myristic acid, palmitic acid, stearic acid, icosanoic acid, (a C20 saturated fatty acid); sodium behenic acid, or an unsaturated fatty acid such as myristoleic acid, palmitoleic acid, oleic acid, sodium linoleic acid, alpha linolenic acid, sodium arachidonic acid, eicosapentanoic acid, and the like. The two fatty acyl residues on the phospholipids may be the same or they may be different fatty acids. The phospholipid component of the drug delivery composition can be either a single phospholipid or a mixture of several phospholipids. The phospholipids should be acceptable for the chosen route of administration.

[0089] In one aspect, the phospholipids used as emulsifiers in the present invention are naturally occurring phospholipids from a natural origin. For example, naturally occurring lecithin is a mixture of the diglycerides of stearic, palmitic, and oleic acids, linked to the choline ester of phosphoric acid, commonly called phosphatidylcholine, and can be obtained from a variety of sources such as eggs and soya beans. Soy lecithin and egg lecithin (including hydrogenated versions of these compounds) have been characterized in various compositions and are generally recognized to be safe, have combined emulsification and solubilization properties, and tend to be broken down into innocuous substances more rapidly than most synthetic surfactants.

[0090] The term "lecithin" includes a complex mixture of acetone-insoluble phosphatides, of which phosphatidylcholine is a significant component. The term lecithin is also used as a synonym for

phosphatidylcholine. Useful lecithins include, but are not limited to, egg yolk-, egg-, soybean-, and corn-derived lecithin. In one embodiment, the emulsifier is lecithin, such as egg yolk-derived lecithin. The terms egg lecithin and egg yolk derived lecithin are used interchangeably throughout. The compositions described herein preferably comprise lecithin as an emulsifier.

[0091] The amount of phospholipids, by weight, in the emulsions of the present disclosure may be within a range of about 10 wt/wt% to about 20 wt/wt%, 11 wt/wt% to 19 wt/wt%, 11 wt/wt% to 15 wt/wt%, 12 wt/wt% to 13 wt/wt%, 13 wt/wt% to 14 wt/wt%, 13 wt/wt% to 20 wt/wt%, or 12 wt/wt% to 18 wt/wt%. In certain embodiments, the phospholipids in the emulsions are at a concentration, by weight, about 11 wt/wt%, 12 wt/wt%, 12.5 wt/wt%, 13 wt/wt%, 13.5 wt/wt%, 14 wt/wt%, 14.5 wt/wt%, or 15 wt/wt%.

[0092] "Oil" refers to an organic liquid of mineral, vegetable, animal, essential or synthetic origin, including, for example, aliphatic or wax-based hydrocarbons, aromatic hydrocarbons or mixed aliphatic and aromatic hydrocarbons.

[0093] The term "buffer" or "buffered" as used herein means a solution containing both a weak acid and its conjugate base, whose pH changes only slightly upon addition of acid or base. As used herein, the phrase "buffering agent" means a species whose inclusion in a solution provides a buffered solution. Buffers are well-known in the art and readily available. Buffers for use according to the methods and compositions described herein include but are not limited to phosphate, citrate, Tris, carbonate, succinate, maleate, borate, MES, Bis-Tris, ADA, aces,PIPES, MOPSO, Bis-Tri Propane, BES, MOPS, TES, HEPES, DIPSO, MOBS, TAPSO, Trizma, HEPPSO, POPSO, TEA, EPPS, Tricine, Gly-Gly, Bicine, GEPBS, TAPS, AMPD, TABS, AMPSO, CHES, CAPSO, AMP, CAPS, and CABS.

[0094] The term "therapeutic agent" describes any natural or synthetic compound which has a biological activity. A "therapeutically effective amount" means the amount that, when administered to an animal or subject for treating or preventing a disorder, condition, or disease, is sufficient to effect treatment for that disorder, condition, or disease.

[0095] As used herein, the term "emesis" includes nausea and vomiting.

[0096] The term "substantially" in reference to a certain feature or entity means to a significant degree or nearly completely (i.e. to a degree of 85% or greater) in reference to the feature or entity.

II. NK-1 RECEPTION ANTAGONIST EMULSION AND METHODS OF MAKING

[0097] The present disclosure is directed to stable pharmaceutical compositions including an NK-1 receptor antagonist, a surfactant or mixtures of surfactants, a co-surfactant, an oil, with an aqueous

phase. The composition can be an injectable emulsion and is in the form of an oil-in-water emulsion which remains stable over an extended period of time and which is suitable for dilution and intravenous administration.

[0098] The NK-1 receptor antagonist compound is present in the oil phase with an emulsifier, a co-surfactant and an oil. The oil phase is then combined with an aqueous phase comprising water and a tonicity agent as described below to generate the stable emulsion. Prior to combining the oil phase with the aqueous phase, the oil phase will have an oil:antagonist compound ratio of about 11:1 to 30:1, 11:1 to 15:1, or about 13:11. For example, in formulating an oil phase comprising aprepitant, use of an oil:aprepitant ratio of about 13:1 was surprisingly found to produce, when mixed with the water phase, an emulsion which is more stable as compared to an emulsion in which the oil phase contains an oil:aprepitant ratio of less than about 12:1 or 11:1, and/or greater than about 15:1, 20:1, or 30:1. Accordingly, in some embodiments the stable emulsion comprising an NK-1 receptor antagonist and to be administered to the subject can have an oil:antagonist compound ratio of about 11:1 to 30:, 11:1 to 15:1, or about 13:11. Also contemplated, however, are emulsions in which the oil:antagonist compound ratio is about 5:1 to 20:1, 5:1 to 15:1 or 5:1 to 10:1.

[0099] Moreover, the present compositions also possess favorable stability properties when the amount of emulsifier in the oil phase is greater than the amount of oil. For example, the oil phase contains an emulsifier:oil ratio of about 5:1 to 1:1, 3:1 to 1:1 or a ratio of about 1.5:1. Such ratios of emulsifier:oil have surprisingly been found to impart greater stability on a final emulsion which is suitable for injection into a patient. For example, an aprepitant emulsion having a phospholipid:oil ratio within the oil phase of about 1.5:1 was found to have greater stability than a similar aprepitant emulsion, wherein the oil phase comprises a phospholipid:oil ratio of about 0.01:1, 0.1:1, 0.5:1 or 0.9:1.

[0100] Suitable NK-1 receptor antagonists for use in the presently described pharmaceutical emulsions include RP 67580 ((3aR,7aR)-Octahydro-2-[1-imino-2-(2-methoxyphenyl)ethyl]-7,7-diphenyl-4H-isoindol)), WIN 51078 (17-β-Hydroxy-17-α-ethynyl-5-α-androstano[3,2-b]pyrimido[1,2-a]benzimidazole), l-733,060, (((2S,3S)-3-[[3,5-bis(Trifluoromethyl) phenyl]methoxy]-2-phenylpiperidine hydrochloride), l-703,606 (cis-2-(Diphenylmethel)-N- ([2-iodophenyl]methyl)-1-azabicyclo(2.2.2)octan-3-amine) MDL 105,212 (R)-1-[2-[3-(3,4-dichlorophenyl)-1-(3,4,5-trimethoxybenzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenylpiperidine-4-carboxamide hydrochloride), serlopitant, maropitant, Antagonist D, aprepitant, fosaprepitant, R116301, CGP49823, CP-96345, CP-99994, GR-203040, MDL-103392, l-760735, SDZ-NKT-343,

nolpitanitium (SR-140333), AV608, rolapitant, SCH 900978, AV608, GSK424887 (GlaxoSmithKline), GSK206136 (GlaxoSmithKline), GR-205171, CP-99994, TAK 637 ((S)-7-(3,5-Bis-trifluoromethyl-benzyl)-9-methyl-5-p-tolyl-8,9,10,11-tetrahydro-7H-1,7,11a-triaza-cycloocta[b]naphthalene-6,12-dione), LY303870 ([(R)-1-[N-(2-methoxybenzyl)acetylamino]-3-(1H-indol-3-yl)-2-[N-(2-(4- (piperidin-1-yl)piperidin-1-yl)acetyl)amino]propane]), LY686017 ((2-chloro-phenyl)-{2-[5-pyridin-4-yl-1-(3,5-bistrifluoromethyl-benzyl)-1H-[1,2,3]triazol-4-yl]-pyridin-3-yl}-methanone), E-6006, casopitant/GW679769 ((2R,4S)-4-(4-acetylpiperazin-1-yl)-N-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl)ethyl]-2-(4-fluoro-2-methylphenyl)-N-methylpiperidine-1-carboxamide), vestipitant, orvepitant and orvepitant maleate, befetupitant, netupitant, ezlopitant, CP-122721, MPC-4505 (Myriad Genetics, Inc.), CP-122721 (Pfizer, Inc.), CJ-1 2,255 (Pfizer, Inc.), SRR 240600 (Sanofi-Aventis), or TA-5538 (Tanabe Seiyaku Co.) including all pharmaceutically acceptable salts thereof.

1. Oil Phase

[0101] The oil (hydrophobic) phase comprises an oil. Triglycerides are exemplary oils for use in the compositions described herein. In certain embodiments the oil is or comprises a vegetable oil. "Vegetable oil" refers to oil derived from plant seeds or nuts. Vegetable oils are typically "long-chain triglycerides" (LCTs), formed when three fatty acids (usually 14 to 22 carbons in length, with unsaturated bonds in varying numbers and locations, depending on the source of the oil) form ester bonds with the three hydroxyl groups on glycerol. In certain embodiments, vegetable oils of highly purified grade (also called "super refined") are used to ensure safety and stability of the oil-in-water emulsions. In certain embodiments hydrogenated vegetable oils, which are produced by controlled hydrogenation of the vegetable oil, may be used. Exemplary vegetable oils include but are not limited to almond oil, babassu oil, black currant seed oil, borage oil, canola oil, castor oil, coconut oil, corn oil, cottonseed oil, olive oil, peanut oil, palm oil, palm kernel oil, rapeseed oil, safflower oil, soybean oil, sunflower oil and sesame oil. Hydrogenated and/or or partially hydrogenated forms of these oils may also be used. In specific embodiments, the oil is or comprises safflower oil, sesame oil, corn oil, olive oil and/or soybean oil. In more specific embodiments, the oil is or comprises safflower oil, and/or soybean oil. The oil is present in the emulsion at about 9 wt/wt%, though this may vary between about 5 wt/wt% to 12 wt/wt% or 9 wt/wt% to 10 wt/wt%.

[0102] To generate the oil phase, the NK-1 receptor antagonist is first mixed with an emulsifier such as a phospholipid emulsifier. Examples 1-6 and 11-19 are examples in which NK-1 receptor antagonist emulsions made using an egg lecithin. A phospholipid emulsifier is added to a

concentration of greater than 10 wt/wt%, 11 wt/wt%, 12 wt/wt% or 13 wt/wt% of the emulsion but less than 15 wt/wt%, 17 wt/wt% or 20 wt/wt% of the emulsion.

[0103] The mixture of antagonist and emulsifier is dissolved in a co-surfactant such as a short chain alcohol (1 to 6 carbons). Examples 1-6 and 11-19 below are some examples in which the co-surfactant is ethanol. The mixture is mixed at an elevated temperature, such as at about 60 °C or 70 °C or at an elevated temperature within the range of about 50 °C or 70 °C, until the NK-1 receptor antagonist and emulsifier are dissolved. This mixture is then combined with the oil, such as soybean oil, by mixing again at an elevated temperature such as at about 60 °C to produce the oil phase containing the NK-1 receptor antagonist. Excess co-surfactant can be removed by standard evaporation methods including heating, or pressure reduction, or a combination thereof such employed in a rotary evaporator. In this process, about 10% to 100%, 20% to 95%, 80% to 100%, 90% to 100%, or 95% to 100% of the ethanol evaporates depending on preparation scale, any pressure reduction, and heating time.

[0104] In one embodiment, the NK-1 receptor antagonist and the emulsifier are dissolved in a co-surfactant and an oil. Examples 1-6 and 11-19 below are some examples in which the co-surfactant is ethanol and the oil is soybean oil, however, the methods can be used with any one or more of the co-surfactants and oils described herein. The mixture is mixed at an elevated temperature, such as at about 60 °C or 70 °C or at an elevated temperature within the range of about 50 °C or 70 °C, at least until the NK-1 receptor antagonist and emulsifier are dissolved to produce the oil phase containing the NK-1 receptor antagonist. The mixture of NK-1 receptor antagonist, emulsifier, co-surfactant and oil are mixed at the elevated temperature for about 15 min to 120 min, about 15 min to 45 min, about 30 min to 90 min, or for about 15 min, 30 min or 50 min.

[0105] Excess co-surfactant can be removed by standard evaporation methods including heating, or pressure reduction, or a combination thereof in a rotary evaporator. During this process, about 10% to 100%, 20% to 95%, 80% to 100%, 90% to 100%, or 95% to 100% of the ethanol evaporates depending on preparation scale, any pressure reduction, and heating time.

[0106] In one embodiment, dexamethasone is added to the oil phase comprising the NK-1 receptor antagonist, emulsifier and oil to generate an oil phase comprising both the NK-1 receptor antagonist and dexamethasone prior to mixing with the aqueous phase to generate the pharmaceutical emulsion for injection. Dexamethasone is added to the oil phase to provide a dose of about 12 mg dexamethasone.

2. Aqueous Phase

[0107] The aqueous phase of the NK-1 receptor antagonist emulsion can be a mixture of water and a tonicity agent, including those such as but not limited to sucrose, mannitol, glycerin or dextrose or a mixture thereof. Also included in the aqueous phase is a pH-modifying agent (pH modifier). Sodium oleate is used in Examples 1-3, 5, 6, and 11-15, and 17-19 below to adjust the pH of the emulsion to about 6 to 9, depending on the desired emulsion formulation. However, it is understood that the pH modifier can be other oleic acids or salts thereof including but not limited to sodium oleate, potassium oleate and ammonium oleate. The oleic acid can comprise about 0.1 wt/wt% to 1.0 wt/wt% or about 0.4 wt/wt% or 0.5 wt/wt% of the stable injectable emulsions as provided herein. The aqueous phase is produced by mixing water with the tonicity agent and pH modifier (e.g., sodium oleate). Additional pH modifiers that may be used include but are not limited to sodium hydroxide, potassium hydroxide, magnesium hydroxide, Tris, sodium carbonate and sodium linoleate. In some embodiments, the pH modifier comprises more than one pH modifier. For example, the aqueous phase may comprise both an oleate and a buffer such as a Tris buffer. The pH modifier used is effective for adjusting the pH of the emulsion to a preferred pH of about 6 to 9, 7 to 8, or about 6, 7, 8 or 9. The aqueous phase can readily form by mixing at room temperature.

[0108] The aqueous phase of the emulsion may further contain a buffering agent to promote stability of the emulsion formulation. The drug substance may degrade; for example, lipophilic drugs will partition into the oil phase, which will confer some degree of protection, but hydrolytic degradation may still occur at the oil-water interface. Possible chemical degradation within parenteral fat emulsions includes oxidation of unsaturated fatty acid residues present in triglyceride and lecithin, and hydrolysis of phospholipids leading to the formation of free fatty acids (FFA) and lysophospholipids. Such degradants lower pH, which may then promote further degradation. Thus, pH should be controlled during manufacture and emulsion formulations may include a buffering agent to provide additional control. Any decrease in pH over the assigned shelf-life may be indicative of chemical degradation. Suitable buffers are well known to the person skilled in the art and include but are not limited to a phosphate buffer, citrate buffer, Tris buffer, carbonate buffer, succinate buffer, maleate buffer or borate buffer. Tris buffer is used in Examples 11 and 19 below to adjust the pH of the emulsion to about 8 to 9. As shown in Examples 11 and 19, in some embodiments a buffer such as Tris buffer can be used in addition to another pH modifier (e.g., oleate or sodium oleate) to adjust or modify the pH of the emulsion. In some embodiments, the buffer is selected from the group, phosphate buffered saline (PBS), modified PBS (PBS-mod) and citrate buffer. In a particular

embodiment, the aqueous phase comprises a buffer, that when mixed with the oil phase will provide a substantially isotonic oil in water emulsion.

[0109] Buffering agents useful for the presently described compositions include, but are not limited to, a phosphate buffer, citrate buffer, Tris buffer, carbonate buffer, succinate buffer, maleate buffer or borate buffer. In a particular embodiment, the buffer is selected from the group, phosphate buffered saline (PBS), modified PBS (PBS-mod) and citrate buffer. In a particular embodiment, the aqueous phase comprises a buffer, that when mixed with the oil phase will provide a substantially isotonic oil in water emulsion. In some embodiments, when the aqueous phase contains a buffering agent, the aqueous phase does not include a tonicity agent. Also, when a buffer is added to the aqueous phase, a pH-adjusting agent may not be added to the aqueous phase. It is understood that a buffer can be added to the aqueous phase or the buffer can be added to the emulsion.

[0110] In some embodiments, the aqueous phase of the emulsion contains a tonicity agent such as sucrose. The tonicity agent is added to an aqueous phase having about 0% to 30%, 0% to 25% or about 20% of the tonicity agent (wt/wt). It was surprisingly found that a composition containing about 20% sucrose wt/wt in the aqueous phase produced an emulsion that was particularly stable as determined by freeze-thaw testing. Accordingly, preferred embodiments include an emulsion in which the aqueous phase comprises a tonicity agent which imparts greater chemical and/or physical stability as compared to an emulsion wherein the aqueous phase contains less than about 10%, 15% or 20% wt/wt tonicity agent or more than about 30%, 40% or 50% wt/wt tonicity agent.

[0111] In one embodiment, the aqueous phase further comprises dexamethasone sodium phosphate (also referred to as "dexamethasone phosphate"). Dexamethasone sodium phosphate is a corticosteroid which is freely soluble in water. Daily dosages for dexamethasone sodium phosphate range from about 0.5 mg to 20 mg, more preferably from about 14 mg to 18 mg or 16 mg, depending on the severity of the disease or disorder. Accordingly, an NK-1 receptor antagonist emulsion further comprising dexamethasone may contain dexamethasone sodium phosphate in the aqueous phase. Accordingly, the aqueous phase of an emulsion suitable for intravenous administration may contain about 0.5 mg to 20 mg, 14 mg to 18 mg or about 16 mg dexamethasone sodium phosphate.

[0112] In another embodiment, a solution of dexamethasone sodium phosphate can be mixed into the fine emulsion prior to sterile filtration to prepare an emulsion containing dexamethasone sodium phosphate in the aqueous phase,

3. Pharmaceutical Emulsion Formulations

[0113] The pharmaceutical compositions comprising NK-1 receptor antagonists as disclosed herein are sterile oil-in-water emulsions comprising the aqueous and oil phases described above. Also encompassed by the disclosure are methods for preparing stable emulsions comprising the receptor antagonist which are suitable for intravenous administration and which can be prepared according to the conventional manufacturing procedures using aseptic techniques.

[0114] The aqueous phase is combined with the oil phase, under high-speed homogenization to produce a coarse emulsion. Examples 1-6 and 12-19 provide examples of NK-1 receptor antagonist emulsions which are produced using compositions and methods disclosed herein. As described in these examples, the combined aqueous and oil phases is homogenized using an IKA Ultra-Turrax T25 dispersing instrument at a speed of 20,000 rpm for 1 min. The speed used in this first homogenization step may vary, for example, from 2000 rpm to 25,000 rpm, or from 15,000 rpm to 22,000 rpm. The time of the homogenization step can also vary, for example, from 0.5 min to 1 hour, or from 1 min to 45 min. This crude emulsion is then homogenized into a fine emulsion by a high-pressure homogenizer, which may be a microfluidizer. The interaction chamber and the cooling coil portions of the microfluidizer are cooled by water, such as by an ice bath. The temperature of the ice bath may be between 0 to 10 °C, or 2 to 6 °C. The temperature of the emulsion coming out of the high-pressure homogenization may be between 0 to 60 °C, 15 °C, to 60 °C, 20 °C to 40 °C, or at about 25 °C. The microfluidizer is first primed with water and then the crude emulsion is introduced. The output from the homogenizer is initially run to waste to remove priming water, and priming water and emulsion mixtures, and then collected in a clean vessel when the stream becomes consistent in appearance. The high-pressure homogenizer cycle may be repeated to sufficiently reduce oil droplet size. The pressure used for the homogenization may vary. The pressures may be between 5000 and 30,000 psi. The number of passes through the microfluidizer may vary in order to achieve the desired droplet size. The number of passes may be from about 2 to 20, 2 to 15, 4 to 15, 4 to 12 or 7 to 8.

[0115] The pharmaceutical formulation may then be passed through a filter system at room temperature, and/or autoclaved, to achieve sterilization. The filters used to achieve sterilization may be chosen by the skilled artisan and may have a nominal pore size of 0.2 μm. The filter material used may vary. In one embodiment, the filter is nylon. In another embodiment, the filter is a Posidyne® filter (covalent charge-modified Nylon 6,6 membrane which exhibits a net positively-charged zeta potential in aqueous solutions). For large scale production the method above may need to be

modified. A skilled practitioner could combine these materials in a different order and using different processing equipment to achieve the desired end result.

[0116] In one embodiment of the disclosure, the homogenization can be done in repeated cycles to achieve an emulsion in which the oil particle/globule size is less than 2 microns (μm) with intermediate cooling of the homogenized product to a temperature less than about 25 °C.

[0117] The final emulsion comprises an oil portion (oil phase) dispersed in an aqueous portion (aqueous phase). The ratio of components to the NK-1 receptor antagonist within the oil phase is an important characteristic of the emulsion which may affect stability of the formulation prepared for injection and each of these ratios within the final pharmaceutical emulsion are presented in more detail below. As described above, the oil phase comprises the NK-1 receptor antagonist, an oil and an emulsifier, examples of which are provided herein.

[0118] The final emulsion contains about 0.7 wt/wt% of the NK-1 receptor antagonist, but may range from about 0.2 wt/wt% to 1.5 wt/wt%, 0.4 wt/wt% to 1.0 wt/wt%, 0.6 wt/wt% to 0.7 wt/wt%, or 0.7 wt/wt% to 0.8 wt/wt%. The emulsion is prepared which can contain about 130 mg of the NK-1 receptor antagonist, however, preparations may also be prepared according to the present disclosure which contain about 100 mg to 1000 mg, 100 mg to 500 mg, 250 mg to 750 mg or 100 mg to 200 mg NK-1 receptor antagonist.

[0119] In one embodiment, the ratio of oil:NK-1 receptor antagonist (wt%:wt%) within the oil phase of the final emulsion is about 13:1 to 14:1, but can range from about 11:1 to 15:1, 12:1 to 14:1, 13:1 to 13.5:1, or 12:1 to 15:1. In another embodiment, the ratio of oil:NK-1 receptor antagonist is about 11:1, 11.5:1, 12:1, 12.5:1, 13:1, 13.5:1, 14:1, 14.5:1 or 15:1.

[0120] The ratio of emulsifier to NK-1 receptor antagonist in the final emulsion can be about 20:1 but may also vary. For example, the ratio of emulsifier:NK-1 receptor antagonist (wt%:wt%) within the oil portion ranges from about 15:1 to 30:1, 20:1 to 25:1, 18:1 to 22:1, 19:1 to 20:1, or 10:1 to 30:1. In one embodiment, the emulsifier:NK-1 receptor antagonist (wt%:wt%) is about 15:1, 18:1, 19:1, 20:1, 21:1, 22:1 or 23:1.

[0121] The ratio of components within the oil phase of the final emulsion may alternatively be expressed in the ratio of (emulsifier plus oil):NK-1 receptor antagonist (wt%:wt%). The ratio of (emulsifier plus oil):NK-1 receptor antagonist can be about 33:1, but the ratios for the present emulsion can range from about 20:1 to 40:1, 25:1 to 35:1, 30:1 to 35:1 or 33:1 to 37:1, or may be, for example, about 30:1, 32:1, 33:1, 34:1, 35:1, 36:1, 37:1, 38:1 or 40:1.

[0122] The composition of the present disclosure has a significant advantage in terms of reduced toxicity as compared to injectable formulations which may contain less desirable excipients such as detergents, e.g., Tween-20 or Tween-80. The present formulations take advantage of the ability to solubilize therapeutically effective amounts of a NK-1 receptor antagonist in an oil phase which can then be used to generate an emulsion suitable for injection. Accordingly, described herein are pharmaceutical emulsion compositions containing a NK-1 receptor antagonist and optionally dexamethasone or dexamethasone sodium phosphate, wherein the emulsion does not comprise a detergent.

[0123] The composition of the present disclosure gives a product suitable for parenteral use because of low particle size. The composition of the present disclosure is easy to use as the product can be diluted with an agent such as an aqueous solution of sucrose, an aqueous solution of maltose or dextrose 5% injection or normal saline to achieve the required concentration for parenteral administration. The composition of the present disclosure also has a prolonged shelf life and hence is suitable for a readily marketable product.

[0124] The compositions of the disclosure are both chemically and physically stable. A physically stable emulsion of the invention is one which can be stored under appropriate conditions for at least 1, 2, 3, 4, 5, 6, 9, 12, 15, 18, 24 or 36 months, without an increase in average droplet size above that allowed as stated in USP <729>. As well, the population of large-diameter fat globules should be within the limits stated in USP <729>.

[0125] Droplet size limits defined in USP <729> apply throughout the assigned shelf life, which for a commercial pharmaceutical formulation may extend to 2-3 years or longer. All true emulsions are thermodynamically unstable and may over time undergo a range of processes which tend to increase the droplet size. These include direct droplet coalescence, when two droplets collide and form a single new droplet, and aggregation, in which droplets adhere together to form larger masses. Aggregation may in some cases be a precursor of further coalescence into larger droplets. These processes may result in large aggregates rising to the surface of the container, a phenomenon known as 'creaming', and ultimately to free oil being visible on the emulsion surface, known as 'cracking'.

[0126] Droplet size limits are typified by USP33-NF28 General Chapter <729> for Globule Size Distribution in Lipid Injectable Emulsions, hereinafter referred to as USP <729>, which defines universal limits for (1) mean droplet size not exceeding 500 nm or 0.5 μm and (2) the population of large-diameter fat globules, expressed as the volume-weighted percentage of fat greater than 5 μm (PFAT5) not exceeding 0.05%, irrespective of the final lipid concentration.

[0127] Droplet size measurements such as those defined in USP<729> can measure the initial increases in size, and hence are predictive of emulsion physical stability, at early times, long before the formulation shows macroscopic visible changes. Accordingly, the emulsions as described herein are stable compositions having an intensity-weighted mean droplet diameter less than about 500 nm, 400 nm, 300 nm, 200 nm or 100 nm.

[0128] The oil or particle droplet size, i.e. diameter, according to the present disclosure is measured using a dynamic light scattering (DLS) instrument, such as the Malvern Zetasizer 4000, Malvern Zetasize Nano S90 or preferably the Malvern Zetasizer Nano ZS. Intensity-weighted particles sizes were recorded, since they do not require the knowledge of the refractive index of the particle. In Malvern Zetasizer instruments, there are two fits for determining the intensity-weighted diameter of the oil droplet size. The first is a cumulant fit that is used to determine the Z-average diameter; this fit can additionally give the polydispersity index (PDI). This cumulant fit is recommended for monodisperse samples possessing a PDI of lower than 0.2. The second is a non-negative least squares (NNLS) fit. This gives the Peak 1 diameter, Peak 2 diameter and Peak 3 diameter. This is more suitable for polydisperse samples having a PDI of greater than 0.2.

[0129] The emulsion preparations as described herein may further comprise a preservative in quantities that preserve the composition. Suitable preservatives used in some of the embodiments of present disclosure include, but are not limited to, disodium edetate, tocopherol, benzalkonium chloride, methyl, ethyl, propyl or butylparaben, benzyl alcohol, phenylethyl alcohol, benzethonium, chlorobutanol, potassium sorbate or combination thereof.

III. MEDICAL USE

[0130] The pharmaceutical compositions of the present disclosure can be used for the prevention or treatment of emesis and provide a non-oral option for patients undergoing highly or moderately emetogenic chemotherapy such as chemotherapy used in cancer patients. The disclosure thus encompasses a method of treatment comprising intravenously administering an emulsion comprising a NK-1 receptor antagonist as described herein to a subject undergoing highly or moderately emetogenic chemotherapy whether the chemotherapy is an initial treatment or repeat courses of the chemotherapy. The pharmaceutical emulsions described herein can be used, for example, in preventing or treating acute and delayed nausea and vomiting associated with the chemotherapy or radiotherapy.

[0131] Another embodiment relates to the use of the pharmaceutical formulations of the disclosure in the manufacture of a medicament for use preventing or treating emesis in a subject in need thereof.

[0132] The amount of the NK-1 receptor antagonist and optionally dexamethasone required for use in the methods of the disclosure may vary with the method of administration and condition of the patient, and the degree of therapy required, and will be ultimately at the discretion of the attendant physician or clinician.

IV. EXAMPLES

The following examples are illustrative in nature and are in no way intended to be limiting.

Example 1: Preparing Aprepitant Emulsions for Intravenous Injection

[0133] To prepare the aprepitant emulsion, an oil phase was first prepared by combining 750 mg of aprepitant and 15.0 g of egg lecithin (LIPOID E 80) with 12.0 ml of ethanol. This mixture was dissolved by heating and stirring at 60 °C and 200 rpm for 15 min. To the resultant solution was added in 10.0 g of soybean oil. Heating at 60 °C and stirring at 200 rpm was continued for another 15 min. The aqueous phase was prepared by dissolving 5.60 g of sucrose and 0.500 g of sodium oleate in 70.0 ml of water for injection. This mixture was stirred at 300 rpm at room temperature for 30 min. The aqueous phase was then added to the oil phase and subsequently subjected to high-speed homogenization (Ultra-Turrax® IKA T25) at a speed of 20,000 rpm for 1 min to produce the crude emulsion. This crude emulsion was then passed 8 times through an ice-cooled high-pressure microfluidizer (Microfluidizer® M-110L, F12Y interaction chamber) at a pressure of 18,000 psi. The resultant fine emulsion was sterilized by passing it through a 0.2 μm nylon syringe filter (Corning). The details of the emulsion composition are provided in Table 1 below. By dynamic light scattering (Malvern® Zetasizer Nano ZS), the intensity-weighted particle size analyzed using non-negative least squares (NNLS) fit gave a Peak 1 diameter of 99 nm. The intensity-weighted mean particle size determined using cumulant fit provided a Z-average diameter of 87 nm. The zeta potential was measured to be -43 mV by laser Doppler micro-electrophoresis (Malvern® Zetasizer Nano ZS). The pH of the injectable emulsion was 8.74. This aprepitant-containing emulsion can be injected as is, or diluted for infusion with 5% dextrose or 0.9% saline.

Table 1

Component	Amount (g)	Concentration (w/w%)	Ratio to Aprepitant
Aprepitant	0.750	0.679	1
Lipoid E 80	15.0	13.6	20
Soybean Oil	10.0	9.05	13.3
Ethanol[1]	8.59	7.78	11.5
Sucrose	5.60	5.07	7.5
Sodium Oleate	0.500	0.453	0.667
Water for Injection	70.0	63.4	93.3
Total	110	100	-

[1]Final amount after taking into account the ethanol that was evaporated during processing.

Example 2: Preparing Aprepitant Emulsions for Intravenous Injection

[0134] To prepare the aprepitant emulsion, an oil phase was first prepared by combining 450 mg of aprepitant and 9.00 g of egg lecithin (LIPOID E 80) with 4.0 ml of ethanol. This mixture was dissolved by heating and stirring at 60 °C and 200 rpm for 15 min. To the resultant solution was added 6.00 g of soybean oil. Heating at 60 °C and stirring at 200 rpm was continued for another 15 min. The aqueous phase was prepared by dissolving 3.36 g of sucrose and 0.300 g of sodium oleate in 42.0 ml of water for injection. This mixture was stirred at 300 rpm at room temperature for 30 min. The aqueous phase was then added to the oil phase and subsequently subjected to high-speed homogenization (Ultra-Turrax® IKA T25) at a speed of 20,000 rpm for 1 min to produce the crude emulsion. This crude emulsion was then passed 8 times through an ice-cooled high-pressure microfluidizer (Microfluidizer® M-110L, F12Y interaction chamber) at a pressure of 18,000 psi. The resultant fine emulsion was sterilized by passing it through a 0.2 μm nylon syringe filter (Corning). The details of the emulsion composition are provided in Table 2 below. By dynamic light scattering (Malvern® Zetasizer Nano ZS), the intensity-weighted particle size analyzed using NNLS fit gave a Peak 1 diameter of 127 nm. The intensity-weighted mean particle sized determined using cumulant fit provided a Z-average diameter of 101 nm. The zeta potential was measured to be -47 mV by laser Doppler micro-electrophoresis (Malvern® Zetasizer Nano ZS). The pH of the injectable emulsion was 8.77. This aprepitant-containing emulsion can be injected as is, or diluted for infusion with 5% dextrose or 0.9% saline.

Table 2

Component	Amount (g)	Concentration (w/w%)	Ratio to Aprepitant
Aprepitant	0.450	0.714	1
Lipoid E 80	9.00	14.3	20
Soybean Oil	6.00	9.52	13.3
Ethanol[1]	1.89	3.00	4.20
Sucrose	3.36	5.33	7.47
Sodium Oleate	0.300	0.476	0.667
Water for Injection	42.0	66.7	93.3
Total	63.0	100	-

[1]Final amount after taking into account the ethanol that was evaporated during processing.

Example 3: Preparing Aprepitant Emulsions for Intravenous Injection

[0135] To prepare the aprepitant emulsion, an oil phase was first prepared by combining 450 mg of aprepitant and 9.00 g of egg lecithin (LIPOID E 80) with 6.0 ml of ethanol. This mixture was dissolved by heating and stirring at 60 °C and 200 rpm for 15 min. To the resultant solution was added in 6.00 g of soybean oil. Heating at 60°C and stirring at 200 rpm was continued for another 15 min. The aqueous phase was prepared by dissolving 15.62 g of sucrose and 0.300 g of sodium oleate in 42.0 ml of water for injection. This mixture was stirred at 300 rpm at room temperature for 30 min. The aqueous phase was then added to the oil phase and subsequently subjected to high-speed homogenization (Ultra-Turrax® IKA T25) at a speed of 20,000 rpm for 1 min to produce the crude emulsion. This crude emulsion was then passed 8 times through an ice-cooled high-pressure microfluidizer (Microfluidizer® M-110L, F12Y interaction chamber) at a pressure of 18,000 psi. The resultant fine emulsion was sterilized by passing it through a 0.2 μm nylon syringe filter (Corning). The details of the emulsion composition are provided in Table 3 below. By dynamic light scattering (Malvern® Zetasizer Nano ZS), the intensity-weighted particle size analyzed using NNLS fit gave a Peak 1 diameter of 88 nm. The intensity-weighted mean particle sized determined using cumulant fit provided a Z-average diameter of 68 nm. The zeta potential was measured to be -42 mV by laser Doppler micro-electrophoresis (Malvern® Zetasizer Nano ZS). The pH of the injectable emulsion was 8.80. This aprepitant-containing emulsion is to be diluted with water for injection by 4-fold prior to injection.

Table 3

Component	Amount (g)	Concentration (w/w%)	Ratio to Aprepitant
Aprepitant	0.450	0.587	1
Lipoid E 80	9.00	11.7	20
Soybean Oil	6.00	7.83	13.3
Ethanol[1]	3.27	4.26	7.26
Sucrose	15.6	20.4	34.7
Sodium Oleate	0.300	0.391	0.667
Water for Injection	42.0	54.8	93.3
Total	76.6	100	-

[1]Final amount after taking into account the ethanol that was evaporated during processing.

Example 4: Preparing an Alternate Aprepitant Emulsion Formulation for Intravenous Injection

[0136] An aprepitant emulsion was prepared which has less than 10% wt/wt of the phospholipid emulsifier and which was adjusted to a pH of less than 8.0. To prepare the aprepitant emulsion, an oil phase was first prepared by combining 450 mg of aprepitant and 6.67 g of egg lecithin (LIPOID E 80) with 7.2 ml of ethanol. This mixture was dissolved by heating and stirring at 60 °C and 200 rpm. Heating and stirring was carried out until the ethanol was evaporated and a thick residue was observed. To the resultant solution was added in 6.00 g of soybean oil and an appropriate amount of ethanol to obtain a clear oil phase upon heating at 60°C. The aqueous phase was prepared by dissolving 3.36 g of sucrose in 50.5 ml of water for injection at 60°C. The aqueous phase was then added to the oil phase and subsequently subjected to high-speed homogenization (Ultra-Turrax® IKA T25) at a speed of 20,000 rpm for 1 min to produce the crude emulsion. The pH of this crude emulsion was adjusted to 7.0 and then passed 8 times through an ice-cooled high-pressure microfluidizer (Microfluidizer® M-110L, F12Y interaction chamber) at a pressure of 18,000 psi. The resultant fine emulsion was sterilized by passing it through a 0.2 µm nylon syringe filter (Corning). The details of the emulsion composition are provided in Table 4 below. Within 4 days post preparation at room temperature, crystals were observed in the product by microscopy.

Table 4

Component	Amount (g)	Concentration (w/w%)	Ratio to Aprepitant
Aprepitant	0.450	0.672	1
Lipoid E 80	6.67	9.95	14.8
Soybean Oil	6.00	8.96	13.3
Sucrose	3.36	5.02	7.47
Water for Injection	50.5	75.4	112
Total	67.0	100	-

Example 5: Preparing Aprepitant Emulsions for Intravenous Injection

[0137] An aprepitant emulsion was prepared which contains oleic acid. To prepare the aprepitant emulsion, an oil phase was first prepared by combining 250 mg of aprepitant, 2.50 g of egg lecithin (LIPOID E 80), 15.0 g of soybean oil and 125 mg of oleic acid. Ten ml of ethanol was added to dissolve the mixture at 70 °C. The ethanol was removed by pressure reduction in a 70 °C water bath to yield a clear oil phase. A preheated aqueous phase containing 82.1 ml of water for injection at 70 °C was added to the oil phase and subsequently subjected to high-speed homogenization (Ultra-Turrax® IKA T25) at a speed of 20,000 rpm for 1 min to produce the crude emulsion. This crude emulsion was passed 8 times through an ice-cooled high-pressure microfluidizer (Microfluidizer® M-110L, F12Y interaction chamber) at a pressure of 18,000 psi. The resultant fine emulsion was sterilized by passing it through a 0.2 µm nylon syringe filter (Corning). The details of the emulsion composition are provided in Table 5 below. Within 4 days post-preparation at room temperature, crystals were observed in the product by microscopy.

Table 5

Component	Amount (g)	Concentration (w/w%)	Ratio to aprepitant
Aprepitant	0.250	0.250	1
Lipoid E 80	2.50	2.50	10
Soybean Oil	15.0	15.0	60
Oleic Acid	0.125	0.125	0.5
Water for Injection	82.1	82.1	328
Total	100	100	-

Example 6: Preparing Emulsions Containing Aprepitant and Dexamethasone Sodium Phosphate for Intravenous Injection

[0138] To prepare an injectable emulsion containing aprepitant and dexamethasone sodium phosphate, an oil phase was first prepared by combining 773 mg of aprepitant and 15.5 g of egg lecithin (LIPOID E 80) with 10.3 ml of ethanol. This mixture was dissolved by heating and stirring at 60 °C and 200 rpm for 15 min. To the resultant solution was added in 10.3 g of soybean oil. Heating at 60 °C and stirring at 200 rpm was continued for another 15 min. The aqueous phase was prepared by dissolving 5.77 g of sucrose and 0.515 g of sodium oleate in 71.1 ml of water for injection. This mixture was stirred at 300 rpm at room temperature for 30 min. The aqueous phase was then added to the oil phase and subsequently subjected to high-speed homogenization (Ultra-Turrax® IKA T25) at a speed of 20,000 rpm for 1 min to produce the crude emulsion. This crude emulsion was then passed 8 times through an ice-cooled high-pressure microfluidizer (Microfluidizer® M-110L, F12Y interaction chamber) at a pressure of 18,000 psi. Dexamethasone sodium phosphate (93.5 mg) dissolved in 1 ml of water for injection was mixed into the fine emulsion. This resultant fine emulsion containing both aprepitant and dexamethasone sodium phosphate was sterilized by passing it through a 0.2 μm nylon syringe filter (Corning). The details of the emulsion composition are provided in Table 6 below. By dynamic light scattering (Malvern® Zetasizer Nano ZS), the intensity-weighted particle size analyzed using NNLS fit gave a Peak 1 diameter of 95 nm. The intensity-weighted mean particle size determined using cumulant fit provided a Z-average diameter of 70 nm. The zeta potential was measured to be -43 mV by laser Doppler micro-electrophoresis (Malvern® Zetasizer Nano ZS). The pH of the injectable emulsion was 8.92. This aprepitant and dexamethasone sodium phosphate containing emulsion can be injected as is, or diluted for infusion with 5% dextrose or 0.9% saline.

Table 6

Component	Amount (g)	Concentration (w/w%)	Ratio to aprepitant
Aprepitant	0.773	0.688	1
Dexamethasone Sodium Phosphate	0.0935	0.0832	0.121
Lipoid E 80	15.5	13.8	20
Soybean Oil	10.3	9.17	13.3
Ethanol[1]	7.31	6.51	9.47
Sucrose	5.77	5.14	7.47
Sodium Oleate	0.515	0.459	0.667
Water for Injection	72.1	64.2	93.3
Total	112	100	-

[1]Final amount after taking into account the ethanol that was evaporated during processing.

Example 7: Stability of the Aprepitant Emulsion at Room Temperature and 5 °C

[0139] Stability of the aprepitant emulsions prepared as described in Examples 1, 2 3 and 6 was measured by incubating each emulsion preparation at room temperature (about 25 °C) or at 5 °C. Mean particle size and percentage of fat globules above 5 μm were measured using DLS and light obscuration respectively to determine if they satisfy USP <729>. The emulsions were also inspected by microscopy for aprepitant crystals. Example 1 was stable at room temperature for 2 months, that is, the mean particle size and percentage of fat globules above 5 μm satisfied USP <729>. Additionally, no aprepitant crystals were visible by microscopy. After 2 months storage at room temperature, creaming was observed in Examples 1 and 6. This corresponded with the observation of aprepitant crystals. Examples 2 and 3 were stable at room temperature for 3 and 2 months respectively. After these time points, aprepitant crystals were observed in these formulations. Storage at 5 °C resulted in longer emulsion stability for Examples 1, 2, 3 and 6. Table 7 shows the characterizations of Examples 1, 2, 3 and 6 and their respective stabilities at room temperature and at 5 °C.

Table 7

Sample	PDI	Particle Size as Peak 1 Diameter (nm)	Particle Size as Z-Average Diameter (nm)	Zeta Potential (mV)	pH	Stability at 25 °C per USP <729> (months)	Stability at 5 °C per USP <729>
Example 1	0.122	99	87	-43	8.74	2	>10 months
Example 2	0.200	127	101	-47	8.77	3	>10 months
Example 3	0.219	88	68	-42	8.80	2	>10 months
Example 6	0.244	95	70	-43	8.92	2	>10 months

Example 8: Stability of the Aprepitant Emulsion to Freeze-Thaw Cycle

[0140] The aprepitant emulsions prepared according to Examples 1, 2, 3 and 6 were tested for stability upon exposure to a freeze-thaw cycle. Samples from the Examples 1, 2, 3 and 6 were stored at -20 °C overnight. They were thawed to room temperature the next day and visualized by microscopy. Prior to freezing, all samples did not present any visible particles under the microscope. FIG. 1 shows microscope images, at 10X, of emulsions after the freeze-thaw cycle (Examples 1, 2, 3 and 6 are shown as FIG. 1 A, B, C, and D, respectively). Emulsions prepared as described in examples 1, 2 and 6 showed visible particles after exposure to freezing. Only Example 3 was stable after freezing. As FIG. 1C shows, no visible particles were observed for the formulation of Example 3. This enhanced stability was conferred by the presence of a large concentration of sucrose (20 w/w% in Example 3 compared to 5 w/wt% in Examples 1, 2 and 6).

Example 9: Pharmacokinetics of an Aprepitant Emulsion

[0141] The pharmacokinetics of an aprepitant emulsion prepared according to Example 1 was determined. Two groups of six male Sprague-Dawley rats each were injected intravenously with, respectively, fosaprepitant in solution or aprepitant emulsion prepared according to Example 1. All drugs were administered at an effective concentration equivalent to 14 mg/kg aprepitant. Blood from all rats was collected at the appropriate time intervals and processed to plasma by centrifugation. Plasma samples were analyzed by LC-MS/MS for aprepitant and fosaprepitant, as appropriate. A plasma concentration versus time curve of aprepitant for the emulsion described in Example 1 and for fosaprepitant is presented in FIG. 2 (fosaprepitant in solution, ●; aprepitant emulsion, ▲). The

curves indicate the initial aprepitant level reached immediately after injection of the aprepitant emulsion was almost 3 times higher than the initial aprepitant level reached immediately after injection of the fosaprepitant solution. Plasma levels of aprepitant resulting from each injection, however, were essentially the same by the 3-hour time point indicating the formulations were bioequivalent except for a delay in the conversion of fosaprepitant to aprepitant.

Example 10: Pharmacokinetics of an Aprepitant and Dexamethasone Emulsion

[0142] The pharmacokinetics of an aprepitant and dexamethasone sodium phosphate combination emulsion prepared according to Example 6 was determined. Male Sprague-Dawley rats each were injected intravenously with fosaprepitant solution (group 1), dexamethasone sodium phosphate solution (group 2), or an emulsion containing aprepitant and dexamethasone sodium phosphate prepared according to Example 6 (group 3). Groups 1 and 2 consisted of six rats each; for group 3, twelve rats were injected with the aprepitant and dexamethasone sodium phosphate combination emulsion to allow for the collection of sufficient samples for the measurement of both active ingredients.

[0143] In groups 1 and 3, a dose was administered at an effective drug concentration equivalent to 2 mg/kg aprepitant. In groups 2 and 3, a dose was administered at an effective drug concentration equivalent to 0.24 mg/kg dexamethasone sodium phosphate. Blood from all rats was collected at the appropriate time intervals and processed to plasma by centrifugation. Plasma samples were analyzed by LC-MS/MS for dexamethasone, aprepitant, and fosaprepitant, as appropriate.

[0144] FIGS. 3 and 4 present the plasma concentration versus time curve of aprepitant and dexamethasone, respectively. FIG. 3 compares the aprepitant plasma concentration versus time curve resulting from injection of the emulsion described in Example 6 (FIG. 3, ●) vs. injection of a solution of fosaprepitant (FIG. 3, ▲). FIG. 4 compares the dexamethasone plasma concentration versus time curve resulting from injection of a dexamethasone sodium phosphate solution (FIG. 4, ●) vs. injection of the emulsion described in Example 6. The curves indicate that the aprepitant in the emulsion is released approximately simultaneously with the dexamethasone sodium phosphate. The presence of dexamethasone sodium phosphate in the emulsion does not affect the pharmacokinetics of aprepitant.

Example 11: Preparing Aprepitant Emulsions for Intravenous Injection

[0145] To prepare the aprepitant emulsion comprising a buffering agent, an oil phase is first prepared by combining 750 mg of aprepitant, 15.0 g of egg lecithin (LIPOID E 80), 10.0 g of soybean oil and 3.75 ml of ethanol. This mixture is dissolved by heating and stirring at 70 °C and 200 rpm for

30 min. The aqueous phase is prepared by dissolving 2.17 g of sucrose and 0.500 g of sodium oleate in a mixture of 4.1 ml of 1M Tris buffer (pH 8.4) and 65.9 ml of water for injection. This mixture is stirred at 300 rpm at room temperature for 30 min. The aqueous phase is then added to the oil phase and subsequently subjected to high-speed homogenization (Ultra-Turrax® IKA T25) at a speed of 20,000 rpm for 1 min to produce the crude emulsion. This crude emulsion is then passed 8 times through an ice-cooled high-pressure microfluidizer (Microfluidizer® M-110L, F12Y interaction chamber) at a pressure of 18,000 psi. The resultant fine emulsion is sterilized by passing it through a 0.2 μm nylon syringe filter (Corning). Dynamic light scattering is used to determine the intensity-weighted particle size using NNLS fit to give the Peak 1 diameter, the intensity-weighted mean particle sized is determined using cumulant fit to provide the Z-average diameter. The zeta potential is measured by laser Doppler micro-electrophoresis (Malvern® Zetasizer Nano ZS). This aprepitant-containing emulsion can be injected as is, or diluted for infusion with 5% dextrose or 0.9% saline.

Example 12: Preparing Rolapitant Emulsions for Intravenous Injection

[0146] To prepare the rolapitant emulsion, an oil phase was first prepared by combining 1.080 g of rolapitant and 21.6 g of egg lecithin (LIPOID E 80) with 14.4 g of soybean oil and 5.40 ml of ethanol in a glass jar. This mixture was allowed to incubate at room temperature for 30 min followed by heating and stirring at 70°C and 200 rpm for another 30 min. The aqueous phase was prepared by dissolving 8.06 g of sucrose and 0.720 g of sodium oleate in 100.8 ml of water for injection by heating and stirring at 35°C and 300 rpm for 15 min. The aqueous phase was then added to the oil phase and subsequently subjected to high-speed homogenization (Ultra-Turrax® IKA T25) at a speed of 20,000 rpm for 1 min to produce the crude emulsion. This crude emulsion was passed 8 times through a high-pressure microfluidizer (Microfluidizer® M-110P, F12Y interaction chamber) at a pressure of 20,000 psi. The outlet fine emulsion temperature was kept at approximately 25°C using cooling water. The resultant fine emulsion was sterilized by passing through a 0.2 μm nylon filter (Nalgene). Details of the emulsion composition are provided in Table 8 below. By dynamic light scattering (Malvern® Zetasizer Nano ZS), the intensity-weighted particle size analyzed using non-negative least squares (NNLS) fit gave a Peak 1 diameter of 127 nm (Table 9). The intensity-weighted mean particle size determined using cumulant fit provided a Z-average diameter of 100 nm. The pH and osmolality of the injectable emulsion were 8.51 and 318 mmol/kg respectively. This rolapitant-containing emulsion can be injected as is, or diluted for infusion with 0.9% saline or 5% dextrose.

Table 8

Component	Amount (g)	Concentration (w/w%)	Ratio to Rolapitant
Rolapitant	1.080	0.728	1
Lipoid E 80	21.6	14.55	20
Soybean Oil	14.4	9.70	13.3
Ethanol[1]	1.78	1.20	1.65
Sucrose	8.06	5.43	7.47
Sodium Oleate	0.720	0.485	0.667
Water for Injection	100.8	67.9	93.3
Total	148	100	-

[1]Final amount after taking into account the ethanol that was evaporated during processing.

Table 9

Sample	PDI	Particle Size as Peak 1 Diameter (nm)	Particle Size as Z-Average Diameter (nm)	pH	Osmolality (mmol/kg)	Stability at 25°C per USP <729>	Stability at 5°C per USP <729>
Example 1	0.213	127	100	8.51	318	>1 months	>1 months

Example 13: Preparing Netupitant Emulsions for Intravenous Injection

[0147] To prepare the emulsion containing a therapeutically effective amount of netupitant, an oil phase is first prepared by combining about 750 mg of netupitant and 15.0 g of egg lecithin (LIPOID E 80) with 12.0 ml of ethanol. This mixture is dissolved by heating and stirring at 60 °C and 200 rpm for 15 min. To the resultant solution is added in 10.0 g of soybean oil. Heating at 60 °C and stirring at 200 rpm is continued for another 15 min. The aqueous phase is prepared by dissolving 5.60 g of sucrose and 0.500 g of sodium oleate in 70.0 ml of water for injection. This mixture is stirred at 300 rpm at room temperature for 30 min. The aqueous phase is then added to the oil phase and subsequently subjected to high-speed homogenization (Ultra-Turrax® IKA T25) at a speed of 20,000 rpm for 1 min to produce the crude emulsion. This crude emulsion is then passed 8 times through an ice-cooled high-pressure microfluidizer (Microfluidizer® M-110L, F12Y interaction chamber) at a pressure of 18,000 psi. The resultant fine emulsion is sterilized by passing it through a 0.2 µm nylon syringe filter (Corning). The details of the emulsion composition are provided in Table 10 below. By dynamic light scattering (Malvern® Zetasizer Nano ZS), the intensity-weighted particle size is analyzed using non-negative least squares (NNLS) fit to obtain a Peak 1 diameter of the particle. The intensity-weighted mean particle size is also determined using cumulant fit and provides a Z-average

diameter. The zeta potential is measured to be -43 mV by laser Doppler micro-electrophoresis (Malvern® Zetasizer Nano ZS). The pH of the injectable emulsion is also measured and is preferably about pH 7.8 to 8.8. This NK-1 receptor antagonist-containing emulsion can be injected as is, or diluted for infusion with 5% dextrose or 0.9% saline.

Table 10

Component	Amount (g)	Concentration (w/w%)	Ratio to Netupitant
Netupitant	0.750	0.679	1
Lipoid E 80	15.0	13.6	20
Soybean Oil	10.0	9.05	13.3
Ethanol[1]	8.59	7.78	11.5
Sucrose	5.60	5.07	7.5
Sodium Oleate	0.500	0.453	0.667
Water for Injection	70.0	63.4	93.3
Total	110	100	-

[1]Final amount after taking into account the ethanol that is evaporated during processing.

Example 14: Preparing Netupitant Emulsions for Intravenous Injection

[0148] To prepare the netupitant emulsion, an oil phase is first prepared by combining about 450 mg of netupitant and 9.00 g of egg lecithin (LIPOID E 80) with 4.0 ml of ethanol. This mixture is dissolved by heating and stirring at 60 °C and 200 rpm for 15 min. To the resultant solution is added 6.00 g of soybean oil. Heating at 60 °C and stirring at 200 rpm is continued for about another 15 min. The aqueous phase is prepared by dissolving 3.36 g of sucrose and 0.300 g of sodium oleate in 42.0 ml of water for injection. This mixture is stirred at 300 rpm at room temperature for 30 min. The aqueous phase is then added to the oil phase and subsequently subjected to high-speed homogenization (Ultra-Turrax® IKA T25) at a speed of 20,000 rpm for 1 min to produce the crude emulsion. This crude emulsion is then passed 8 times through an ice-cooled high-pressure microfluidizer (Microfluidizer® M-110L, F12Y interaction chamber) at a pressure of 18,000 psi. The resultant fine emulsion is sterilized by passing it through a 0.2 µm nylon syringe filter (Corning). The details of the emulsion composition are provided in Table 11 below. By dynamic light scattering (Malvern® Zetasizer Nano ZS), the intensity-weighted particle size is analyzed using NNLS fit to give a Peak 1 diameter. The intensity-weighted mean particle size is determined using cumulant fit provides a Z-average diameter. The zeta potential is measured by laser Doppler micro-electrophoresis (Malvern® Zetasizer Nano ZS). The pH of the injectable emulsion is also measured and is preferably

about pH 7.8 to 8.8. This netupitant-containing emulsion can be injected as is, or diluted for infusion with 5% dextrose or 0.9% saline.

Table 11

Component	Amount (g)	Concentration (w/w%)	Ratio to Netupitant
Netupitant	0.450	0.714	1
Lipoid E 80	9.00	14.3	20
Soybean Oil	6.00	9.52	13.3
Ethanol[1]	1.89	3.00	4.20
Sucrose	3.36	5.33	7.47
Sodium Oleate	0.300	0.476	0.667
Water for Injection	42.0	66.7	93.3
Total	63.0	100	-

[1]Final amount after taking into account the ethanol that is evaporated during processing.

Example 15: Preparing Netupitant Emulsions for Intravenous Injection

[0149] To prepare the netupitant emulsion, an oil phase is first prepared by combining 450 mg of netupitant and 9.00 g of egg lecithin (LIPOID E 80) with 6.0 ml of ethanol. This mixture is dissolved by heating and stirring at 60 °C and 200 rpm for 15 min. To the resultant solution is added in 6.00 g of soybean oil. Heating at 60°C and stirring at 200 rpm is continued for another 15 min. The aqueous phase is prepared by dissolving 15.62 g of sucrose and 0.300 g of sodium oleate in 42.0 ml of water for injection. This mixture is stirred at 300 rpm at room temperature for 30 min. The aqueous phase is then added to the oil phase and subsequently subjected to high-speed homogenization (Ultra-Turrax® IKA T25) at a speed of 20,000 rpm for 1 min to produce the crude emulsion. This crude emulsion is then passed 8 times through an ice-cooled high-pressure microfluidizer (Microfluidizer® M-110L, F12Y interaction chamber) at a pressure of 18,000 psi. The resultant fine emulsion is sterilized by passing it through a 0.2 µm nylon syringe filter (Corning). The details of the emulsion composition are provided in Table 12 below. By dynamic light scattering (Malvern® Zetasizer Nano ZS), the intensity-weighted particle size is analyzed using NNLS fit gave a Peak 1 diameter. The intensity-weighted mean particle size is determined using cumulant fit provided a Z-average diameter. The zeta potential is measured by laser Doppler micro-electrophoresis (Malvern® Zetasizer Nano ZS). The pH of the injectable emulsion is also measured and is preferably about pH 7.8 to 8.8. This netupitant-containing emulsion is to be diluted with water for injection by 4-fold prior to injection.

Table 12

Component	Amount (g)	Concentration (w/w%)	Ratio to Netupitant
Netupitant	0.450	0.587	1
Lipoid E 80	9.00	11.7	20
Soybean Oil	6.00	7.83	13.3
Ethanol[1]	3.27	4.26	7.26
Sucrose	15.6	20.4	34.7
Sodium Oleate	0.300	0.391	0.667
Water for Injection	42.0	54.8	93.3
Total	76.6	100	-

[1]Final amount after taking into account the ethanol that is evaporated during processing.

Example 16: Alternate Netupitant Emulsion Formulations for Intravenous Injection

[0150] A netupitant emulsion is prepared which has less than 10% wt/wt of the phospholipid emulsifier and which is adjusted to a pH of less than 8.0. To prepare the netupitant emulsion, an oil phase is first prepared by combining 450 mg of netupitant and 6.67 g of egg lecithin (LIPOID E 80) with 7.2 ml of ethanol. This mixture is dissolved by heating and stirring at 60 °C and 200 rpm. Heating and stirring is carried out until the ethanol is evaporated and a thick residue is observed. To the resultant solution is added in 6.00 g of soybean oil and an appropriate amount of ethanol to obtain a clear oil phase upon heating at 60°C. The aqueous phase is prepared by dissolving 3.36 g of sucrose in 50.5 ml of water for injection at 60°C. The aqueous phase is then added to the oil phase and subsequently subjected to high-speed homogenization (Ultra-Turrax® IKA T25) at a speed of 20,000 rpm for 1 min to produce the crude emulsion. The pH of this crude emulsion is adjusted to 7.0 and then passed 8 times through an ice-cooled high-pressure microfluidizer (Microfluidizer® M-110L, F12Y interaction chamber) at a pressure of 18,000 psi. The resultant fine emulsion is sterilized by passing it through a 0.2 µm nylon syringe filter (Corning). The details of the emulsion composition are provided in Table 13 below. Within 4 days post preparation at room temperature, the emulsion product is analyzed for the presence of crystals by microscopy.

Table 13

Component	Amount (g)	Concentration (w/w%)	Ratio to Netupitant
Netupitant	0.450	0.672	1

Lipoid E 80	6.67	9.95	14.8
Soybean Oil	6.00	8.96	13.3
Sucrose	3.36	5.02	7.47
Water for Injection	50.5	75.4	112
Total	67.0	100	-

Example 17: Alternate Netupitant Emulsion Formulations for Intravenous Injection

[0151] A netupitant emulsion is prepared which contains oleic acid. To prepare the netupitant emulsion, an oil phase is first prepared by combining 250 mg of netupitant, 2.50 g of egg lecithin (LIPOID E 80), 15.0 g of soybean oil and 125 mg of oleic acid. Ten ml of ethanol is added to dissolve the mixture at 70 °C. The ethanol is removed by pressure reduction in a 70 °C water bath to yield a clear oil phase. A preheated aqueous phase containing 82.1 ml of water for injection at 70 °C is added to the oil phase and subsequently subjected to high-speed homogenization (Ultra-Turrax® IKA T25) at a speed of 20,000 rpm for 1 min to produce the crude emulsion. This crude emulsion is passed 8 times through an ice-cooled high-pressure microfluidizer (Microfluidizer® M-110L, F12Y interaction chamber) at a pressure of 18,000 psi. The resultant fine emulsion is sterilized by passing it through a 0.2 µm nylon syringe filter (Corning). The details of the emulsion composition are provided in Table 14 below. Within 4 days post preparation at room temperature, the emulsion product is analyzed for the presence of crystals by microscopy.

Table 14

Component	Amount (g)	Concentration (w/w%)	Ratio to Netupitant
Netupitant	0.250	0.250	1
Lipoid E 80	2.50	2.50	10
Soybean Oil	15.0	15.0	60
Oleic Acid	0.125	0.125	0.5
Water for Injection	82.1	82.1	328
Total	100	100	-

Example 18: Preparing Emulsions Containing Netupitant and Dexamethasone Sodium Phosphate for Intravenous Injection

[0152] To prepare an injectable emulsion containing netupitant and dexamethasone sodium phosphate, an oil phase are first prepared by combining 773 mg of netupitant and 15.5 g of egg lecithin (LIPOID E 80) with 10.3 ml of ethanol. This mixture is dissolved by heating and stirring at 60 °C and 200 rpm for 15 min. To the resultant solution is added in 10.3 g of soybean oil. Heating at 60 °C and stirring at 200 rpm is continued for another 15 min. The aqueous phase is prepared by dissolving 5.77 g of sucrose and 0.515 g of sodium oleate in 71.1 ml of water for injection. This mixture is stirred at 300 rpm at room temperature for 30 min. The aqueous phase is then added to the oil phase and subsequently subjected to high-speed homogenization (Ultra-Turrax® IKA T25) at a speed of 20,000 rpm for 1 min to produce the crude emulsion. This crude emulsion is then passed 8 times through an ice-cooled high-pressure microfluidizer (Microfluidizer® M-110L, F12Y interaction chamber) at a pressure of 18,000 psi. Dexamethasone sodium phosphate (93.5 mg) dissolved in 1 ml of water for injection is mixed into the fine emulsion. This resultant fine emulsion containing both netupitant and dexamethasone sodium phosphate is sterilized by passing it through a 0.2 µm nylon syringe filter (Corning). The details of the emulsion composition are provided in Table 15 below. By dynamic light scattering (Malvern® Zetasizer Nano ZS), the intensity-weighted particle size is analyzed using NNLS fit to determine a Peak 1 diameter. The intensity-weighted mean particle size is determined using cumulant fit to determine a Z-average diameter. The zeta potential is measured to be -43 mV by laser Doppler micro-electrophoresis (Malvern® Zetasizer Nano ZS). The preferred pH of the injectable emulsion is between about 8.5 and 9.5. This netupitant and dexamethasone sodium phosphate containing emulsion can be injected as is, or diluted for infusion with 5% dextrose or 0.9% saline.

Table 15

Component	Amount (g)	Concentration (w/w%)	Ratio to Netupitant
Netupitant	0.773	0.688	1
Dexamethasone Sodium Phosphate	0.0935	0.0832	0.121
Lipoid E 80	15.5	13.8	20
Soybean Oil	10.3	9.17	13.3
Ethanol[1]	7.31	6.51	9.47
Sucrose	5.77	5.14	7.47
Sodium Oleate	0.515	0.459	0.667
Water for Injection	72.1	64.2	93.3
Total	112	100	-

[1]Final amount after taking into account the ethanol that is evaporated during processing.

Example 19: Preparing NK-1 Receptor Antagonist Emulsions for Intravenous Injection

[0153] To prepare an NK-1 receptor antagonist emulsion comprising a buffering agent, an oil phase is first prepared by combining 750 mg of aprepitant, 15.0 g of egg lecithin (LIPOID E 80), 10.0 g of soybean oil and 3.75 ml of ethanol. This mixture is dissolved by heating and stirring at 70 °C and 200 rpm for 30 min. The aqueous phase is prepared by dissolving 2.17 g of sucrose and 0.500 g of sodium oleate in a mixture of 4.1 ml of 1M Tris buffer (pH 8.4) and 65.9 ml of water for injection. This mixture is stirred at 300 rpm at room temperature for 30 min. The aqueous phase is then added to the oil phase and subsequently subjected to high-speed homogenization (Ultra-Turrax® IKA T25) at a speed of 20,000 rpm for 1 min to produce the crude emulsion. This crude emulsion is then passed 8 times through an ice-cooled high-pressure microfluidizer (Microfluidizer® M-110L, F12Y interaction chamber) at a pressure of 18,000 psi. The resultant fine emulsion is sterilized by passing it through a 0.2 µm nylon syringe filter (Corning). Dynamic light scattering is used to determine the intensity-weighted particle size using NNLS fit to give the Peak 1 diameter, the intensity-weighted mean particle sized is determined using cumulant fit to provide the Z-average diameter. The zeta potential is measured by laser Doppler micro-electrophoresis (Malvern® Zetasizer Nano ZS). This aprepitant-containing emulsion can be injected as is, or diluted for infusion with 5% dextrose or 0.9% saline.

Example 20: Stability of the Rolapitant Emulsion at Room Temperature and 5 °C

[0154] Stability of the rolapitant emulsion prepared as described in Example 12 was measured by incubating the emulsion preparation at room temperature (about 25 °C) or at 5 °C. Mean particle size and percentage of fat globules above 5 μm were measured using DLS and light obscuration respectively and demonstrated to satisfy USP <729> after 2 months of storage. The emulsions were also inspected by microscopy for rolapitant crystals and visually for the presence of emulsion creaming. The absence of crystals or emulsion creaming further indicated product stability.

Example 21: Stability of the Netupitant Emulsion at Room Temperature and 5 °C

[0155] Stability of the netupitant emulsions prepared as described in Examples 13-17 can be measured by incubating each emulsion preparation at room temperature (about 25 °C) or at 5 °C. Mean particle size and percentage of fat globules above 5 μm are measured using DLS and light obscuration respectively to determine if they satisfy USP <729>. The emulsions are also inspected by microscopy for netupitant crystals and/or visually for the presence of emulsion creaming. The absence of crystals or emulsion creaming indicates product stability.

Example 22: Stability of the Netupitant Emulsion to Freeze-Thaw Cycle

[0156] The netupitant emulsions prepared according to Examples 13-17 can be tested for stability upon exposure to a freeze-thaw cycle. Samples from the Examples 13-17 are stored at -20 °C overnight. The absence of visible particles when the samples are viewed under a microscope indicates product stability.

[0157] While a number of exemplary aspects and embodiments have been discussed above, those of skill in the art will recognize certain modifications, permutations, additions and sub-combinations thereof. It is therefore intended that the following appended claims and claims hereafter introduced are interpreted to include all such modifications, permutations, additions and sub-combinations as are within their true spirit and scope.

WHAT IS CLAIMED IS:

1. An injectable pharmaceutical emulsion, comprising:
about 0.7-0.8 wt% aprepitant;
an emulsifier;
an oil;
a co-surfactant; and
water,
wherein the ratio of the emulsifier to aprepitant ranges from about 20:1 to 25:1 (wt/wt%).

2. The emulsion of claim 1, wherein the emulsifier is a phospholipid.

3. The emulsion of claim 2, wherein the phospholipid is present in the emulsion at about 16 wt/wt%.

4. The emulsion of claim 2, wherein the phospholipid is present in the emulsion at about 17 wt/wt%.

5. The emulsion of claim 1, wherein the emulsifier is an egg lecithin.

6. The emulsion of claim 5, wherein the egg lecithin is present in the emulsion at about 16 wt/wt%.

7. The emulsion of claim 5, wherein the phospholipid is present in the emulsion at about 17 wt/wt%.

8. The emulsion of claim 1, wherein the oil is selected from the group consisting of coconut oil, olive oil, soybean oil, safflower oil, triglycerides, octyl and decyl glycerate, ethyl oleate, glyceryl linoleate, ethyl linoleate, glyceryl oleate, cholesteryl oleate, cholesteryl linoleate, and mixtures thereof.

9. The emulsion of claim 8, wherein the oil is present at a concentration of about 9 wt/wt % to 10 wt/wt %.

10. The emulsion of claim 1, wherein the co-surfactant comprises an alcohol.

11. The emulsion of claim 10, wherein the alcohol is present in the emulsion at less than 10 wt/wt%.

12. The emulsion of claim 10, wherein the co-surfactant is ethanol.

13. The emulsion of claim 1, further comprising an osmotic agent.

14. The emulsion of claim 13, wherein the osmotic agent is selected from the group consisting of glycerol, sorbitol, xylitol, mannitol, glucose, trehalose, maltose, sucrose, raffinose, lactose, dextran, polyethylene glycol, or propylene glycol.

15. The emulsion of claim 14, wherein the osmotic agent is present at a concentration of about 3 wt/wt % to 8 wt/wt %.

16. The emulsion of claim 1, further comprising a pH modifier.

17. The emulsion of claim 16, wherein the pH modifier is oleic acid or a salt thereof.

18. The emulsion of claim 1, wherein the emulsifier is egg lecithin.

19. The emulsion of claim 1, wherein the co-surfactant is ethanol.

20. The emulsion of claim 1, further comprising sucrose.

21. The emulsion of claim 1, further comprising sodium oleate

22. An injectable pharmaceutical emulsion, comprising:
about 0.7-0.8 wt% aprepitant;
an emulsifier;
an oil;
a co-surfactant; and
water,
wherein the ratio of the emulsifier to aprepitant ranges about 23:1 (wt/wt%).

23. The emulsion of claim 22, wherein the emulsifier is a phospholipid.

24. The emulsion of claim 23, wherein the phospholipid is selected from the group consisting of egg phospholipids and soy phospholipids.

25. The emulsion of claim 22, wherein the oil is selected from the group consisting of coconut oil, olive oil, soybean oil, safflower oil, triglycerides, octyl and decyl glycerate, ethyl oleate, glyceryl linoleate, ethyl linoleate, glyceryl oleate, cholesteryl oleate, cholesteryl linoleate, and mixtures thereof.

26. The emulsion of claim 22, wherein the co-surfactant comprises an alcohol present in the emulsion at less than 10 wt/wt%.

27. An injectable pharmaceutical emulsion, comprising:
about 0.7-0.8 wt% aprepitant;
an emulsifier;
an oil;
a co-surfactant; and
water,
wherein the ratio of the emulsifier to aprepitant ranges about 24:1 (wt/wt%).

28. The emulsion of claim 27, wherein the emulsifier is a phospholipid.

29. The emulsion of claim 27, wherein the phospholipid is selected from the group consisting of egg phospholipids and soy phospholipids.

30. The emulsion of claim 27, wherein the oil is selected from the group consisting of coconut oil, olive oil, soybean oil, safflower oil, triglycerides, octyl and decyl glycerate, ethyl oleate, glyceryl linoleate, ethyl linoleate, glyceryl oleate, cholesteryl oleate, cholesteryl linoleate, and mixtures thereof.

ABSTRACT OF THE DISCLOSURE

Disclosed herein are novel pharmaceutical formulations of a neurokinin-1 (NK-1) receptor antagonist suitable for parenteral administration including intravenous administration. Also included are formulations including both the NK-1 receptor antagonist and dexamethasone sodium phosphate. The pharmaceutical formulations are stable oil-in-water emulsions for non-oral treatment of emesis and are particularly useful for treatment of subjects undergoing highly emetogenic cancer chemotherapy.

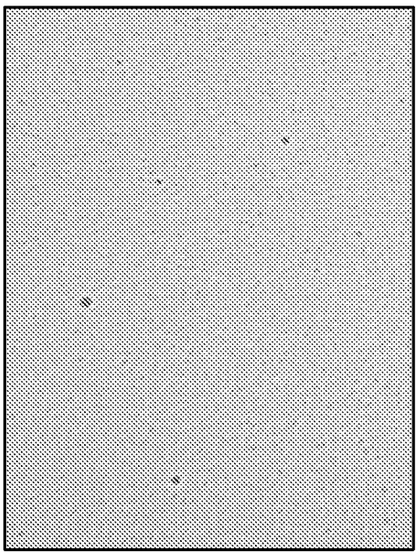


FIG. 1A

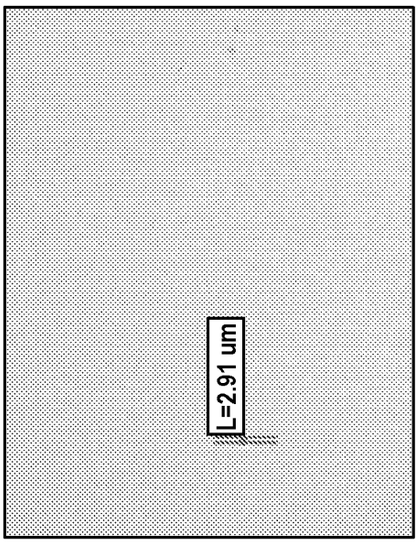


FIG. 1B

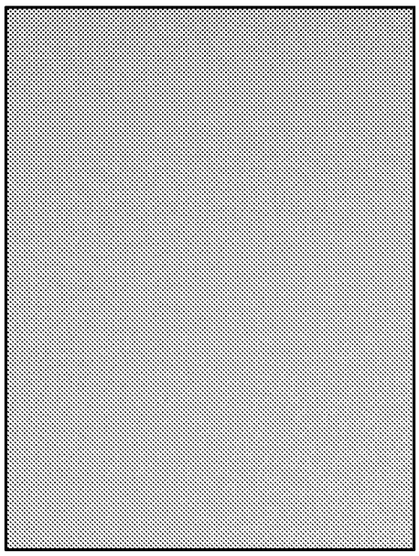


FIG. 1C

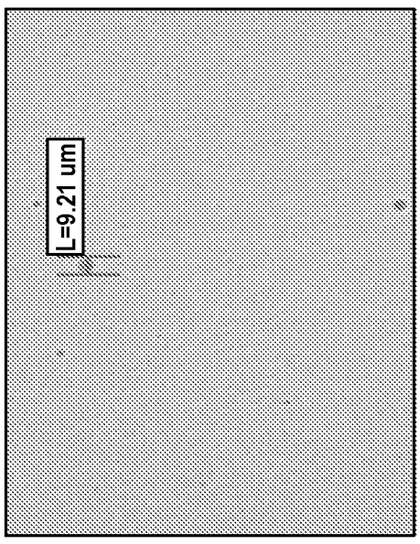


FIG. 1D

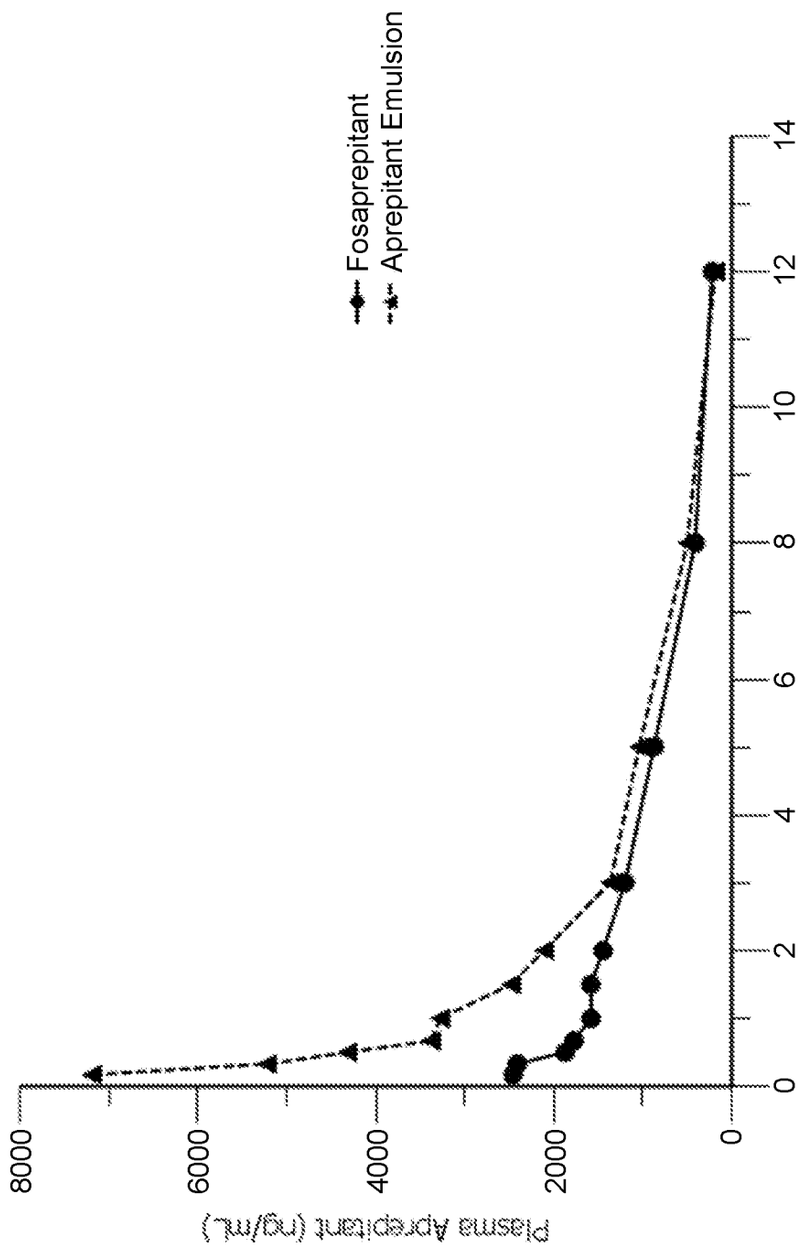

Fosaprepitant
Aprepitant Emulsion
Plasma Aprepitant (ng/mL)
8000
6000
4000
2000
0
0
2
4
6
8
10
12
14
Hours

FIG. 2

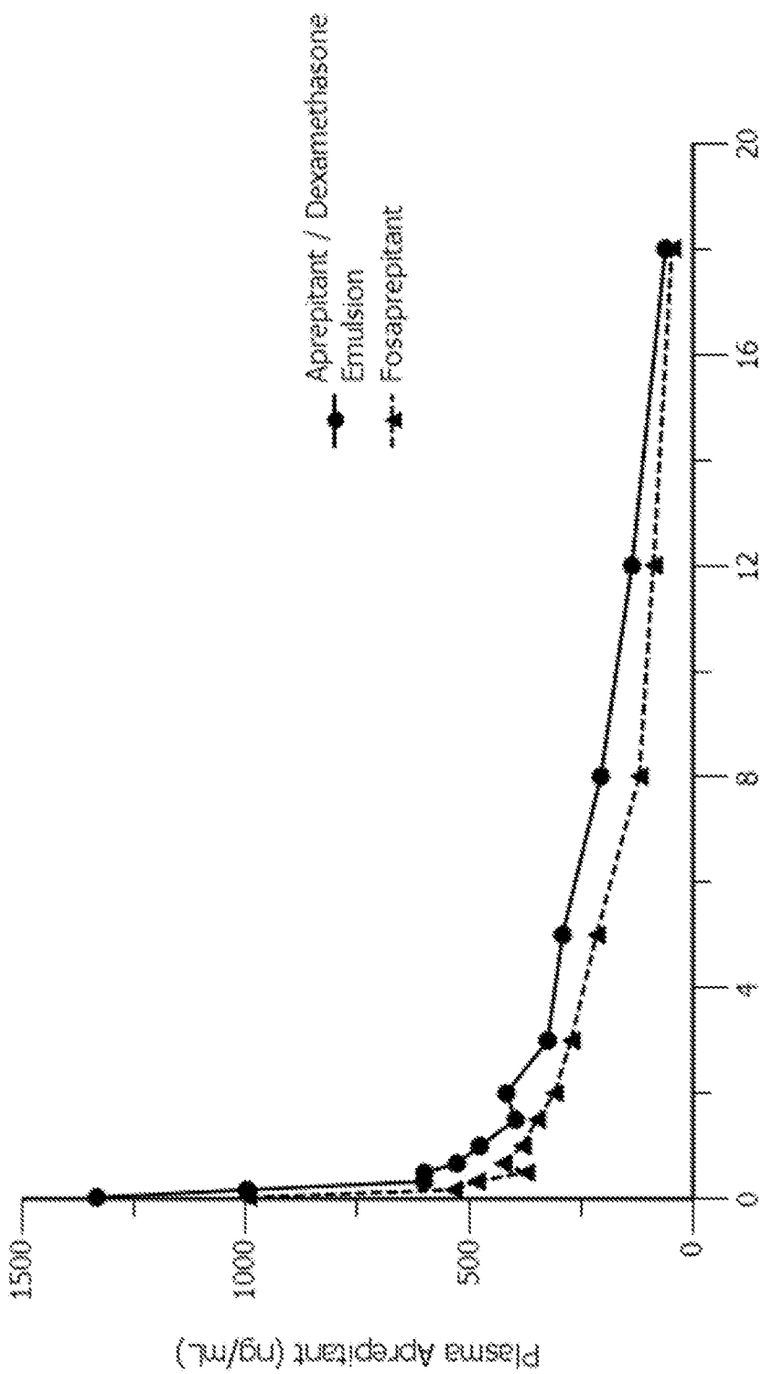

Aprepitant / Dexamethasone Emulsion
Fosaprepitant
Plasma Aprepitant (ng/mL)
1500
1000
500
0
0
4
8
12
16
20
Hours

FIG. 3

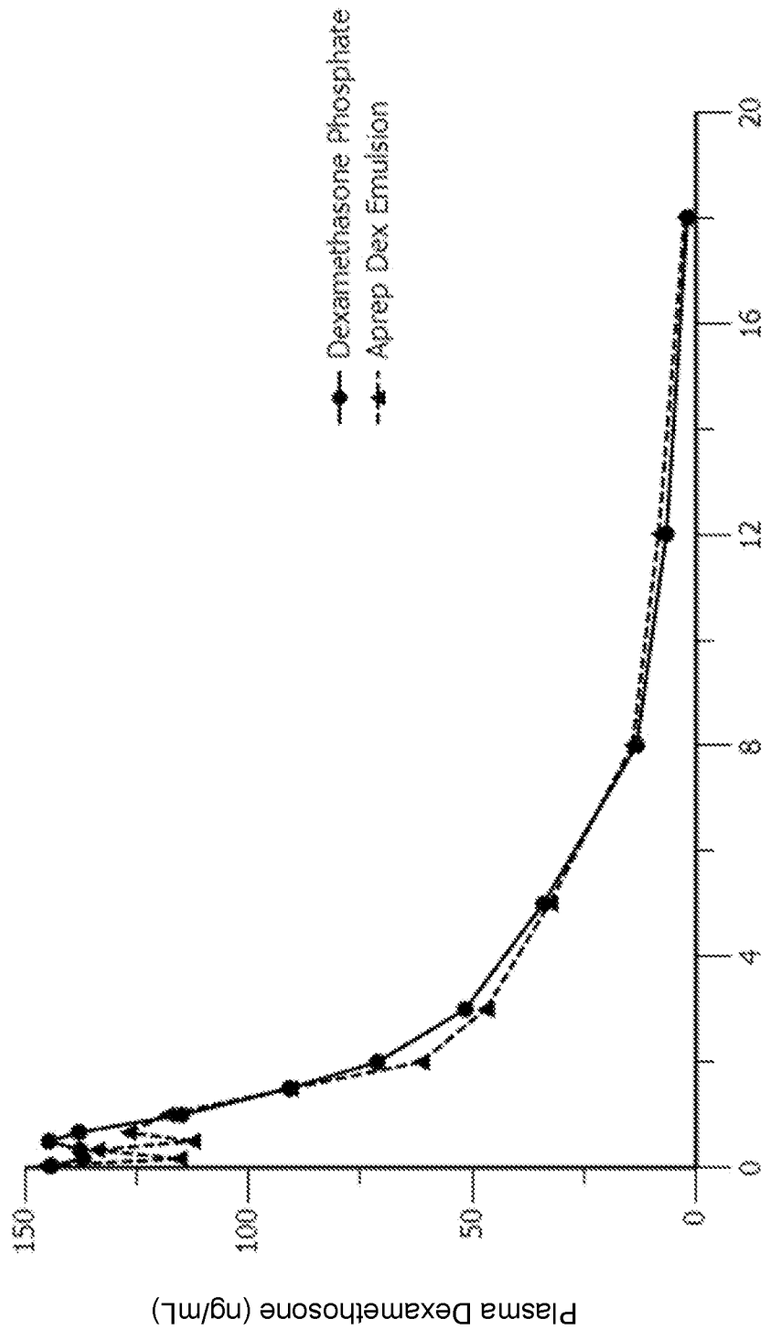

Dexamethasone Phosphate
Aprep Dex Emulsion
Plasma Dexamethosone (ng/mL)
150
100
50
0
0
4
8
12
16
20
Hours

FIG. 4

PTO/AIA/01 (06-12)
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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	EMULSION FORMULATIONS OF AN NK-1 RECEPTOR ANTAGONIST AND USES THEREOF

As the below named inventor, I hereby declare that:

This declaration is directed to:

- [■] The attached application, or
- [ ] United States application or PCT international application number _____

filed on _____.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: Thomas B. Ottoboni Date (Optional): FEB-1-2016

Signature: _____

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 1 minute to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	EMULSION FORMULATIONS OF AN NK-1 RECEPTOR ANTAGONIST AND USES THEREOF

As the below named inventor, I hereby declare that:

This declaration is directed to:

- [■] The attached application, or
- [ ] United States application or PCT international application number _____

filed on _____.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

WARNING:

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LEGAL NAME OF INVENTOR

Inventor: Han Han Date (Optional) :_____

Signature: _____

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 1 minute to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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POWER OF ATTORNEY TO PROSECUTE APPLICATIONS BEFORE THE USPTO

I hereby revoke all previous powers of attorney given in the application identified in the attached statement under 37 CFR 3.73(c).

I hereby appoint:

[X] Practitioners associated with Customer Number: 108547

OR

[ ] Practitioner(s) named below (if more than ten patent practitioners are to be named, then a customer number must be used):

Name	Registration Number	Name	Registration Number

As attorney(s) or agent(s) to represent the undersigned before the United States Patent and Trademark Office (USPTO) in connection with any and all patent applications assigned only to the undersigned according to the USPTO assignment records or assignment documents attached to this form in accordance with 37 CFR 3.73(c).

Please change the correspondence address for the application identified in the attached statement under 37 CFR 3.73(c) to:

[X] The address associated with Customer Number: 108547

OR

[ ]

Firm or individual name		
Address		
City	State	Zip
Country		
Telephone	Email	

Assignee name and address: Heron Therapeutics, Inc.
4242 Campus Point Court, Suite 200
San Diego, CA 92121

A copy of this form, together with a statement under 37 CFR 3.73(c) (Form PTO/AIA/96 or equivalent) is required to be filed in each application in which this form is used. The statement under 37 CFR 3.73(c) may be completed by one of the practitioners appointed in this form, and must identify the application in which this Power of Attorney is to be filed.

SIGNATURE of Assignee of Record

The individual whose signature and title is supplied below is authorized to act on behalf of the assignee.

Signature DocuSigned by: Thomas Ottoboni	Date January 10, 2019 | 1:28 PM PST
Name Thomas B. Ottoboni	Telephone (650) 366-2626
Title Senior Vice President, Pharmaceutical and Translational Sciences; Chief Scientific Officer	

This collection of information is required by 37 CFR 1.31, 1.32, and 1.33. The information is required to obtain or retain a benefit by the public, which is to update (and by the USPTO to process) the file of a patent or reexamination proceeding. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 18 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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STATEMENT UNDER 37 CFR 3.73(c)

First Named Inventor/Patent Owner: Heron Therapeutics, Inc.

Application No./Patent No.: To be assigned Filed/Issue Date: Herewith

Titled: METHODS OF USE OF EMULSION FORMULATIONS OF AN NK-1 RECEPTOR ANTAGONIST

Heron Therapeutics, Inc., a Corporation

(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that, for the patent application/patent identified above, it is (choose **one** of options 1, 2, 3 or 4 below):

1. ☑ The assignee of the entire right, title, and interest.

2. ☐ An assignee of less than the entire right, title, and interest (check applicable box):

   ☐ The extent (by percentage) of its ownership interest is _____%. Additional Statement(s) by the owners holding the balance of the interest must be submitted to account for 100% of the ownership interest.

   ☐ There are unspecified percentages of ownership. The other parties, including inventors, who together own the entire right, title and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

3. ☐ The assignee of an undivided interest in the entirety (a complete assignment from one of the joint inventors was made). The other parties, including inventors, who together own the entire right, title, and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

4. ☐ The recipient, via a court proceeding or the like (*e.g.*, bankruptcy, probate), of an undivided interest in the entirety (a complete transfer of ownership interest was made). The certified document(s) showing the transfer is attached.

The interest identified in option 1, 2 or 3 above (not option 4) is evidenced by either (choose **one** of options A or B below):

A. ☑ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel 052128, Frame 0548, or for which a copy thereof is attached*.

B. ☐ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: _____ To: _____

   The document was recorded in the United States Patent and Trademark Office at

   Reel _____, Frame _____, or for which a copy thereof is attached*.

2. From: _____ To: _____

   The document was recorded in the United States Patent and Trademark Office at

   Reel _____, Frame _____, or for which a copy thereof is attached*.

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STATEMENT UNDER 37 CFR 3.73(c)

3. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached*.

4. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached*.

5. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached*.

6. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached*.

☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

☑ *As required by 37 CFR 3.73(c)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (i.e., a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

/Peter Brunovskis/	2024-01-09
Signature	Date
Peter Brunovskis	52441
Printed or Typed Name	Title or Registration Number

ASSIGNMENT

THIS ASSIGNMENT is by Thomas B. Ottoboni and Han Han (the "Assignors"), residing in Belmont, California and Sunnyvale, California, respectively. We, the Assignors, have invented certain inventions (the "Invention(s)") described in a United States Patent Application entitled EMULSION FORMULATIONS OF AN NK-1 RECEPTOR ANTAGONIST AND USES THEREOF (the "Application") bearing Application No. 15/012,532, with a filing date of February 1, 2016.

JMM 4.30.19

4242 Campus Point Court, Suite 200

HERON THERAPEUTICS, INC., having a place of business at ~~123 Saginaw Drive~~, JMM 4.30.19 San Diego 92121 ~~Redwood City~~, CA ~~94063~~ ("Assignee"), desires to acquire the entire right, title and interest in and to the Inventions and the Application, and in and to any patents (collectively, "Patents") that may be granted for the Inventions in the United States or in any foreign countries.

For valuable consideration, the receipt and sufficiency of which we acknowledge, Assignors hereby sell, assign, and transfer to Assignee, its successors, legal representatives and assigns, the entire right, title and interest in and to: the Inventions, the Application, and any Patents; any divisions, continuations, and continuations-in-part of the Application and any other application claiming priority rights from the Application; any reissues, reexaminations, or extensions of any and all Patents; the right to file foreign applications directly in the name of Assignee; and the right to claim priority rights deriving from the Application (collectively, the "Rights"). Assignors warrant that they are the owners of the Rights, and that the Rights are unencumbered. Assignors also agree to not sign any writing or do any act conflicting with this assignment, and, without further compensation, to sign all documents and do such additional acts as Assignee deems necessary or desirable to: perfect Assignee's enjoyment of the Rights; prepare and prosecute the Application or any other applications for Patents; conduct proceedings regarding the Rights, including any litigation or interference proceedings; or perfect or defend title to the Rights.

[The remainder of this page is intentionally left blank.]

Assignors request the Commissioner of Patents to issue any Patent of the United States that may be issued on the Inventions to Assignee. This Assignment may be executed in counterparts.

Date: April 6 2016

Thomas B. Ottoboni

Date: April 6 2016

Han Han

WITNESSES TO SIGNATURE BY THOMAS B. OTTOBONI

1. _____ April 6, 2016
Signature Date

KHYLA LE
Print Name

119 POPPY CT
Street Address

MILLPITAS, CA 95035
City, Country & Postal Code

2. _____ 06 APR 2016
Signature Date

Jason Cutes
Print Name

263 Stanley Ave
Street Address

Pacifica, CA 94044
City, Country & Postal Code

OR

STATE OF _____

COUNTY OF _____

On _____ before me, _____, personally appeared **Thomas B. Ottoboni**, personally known to me (or proved to me on the basis of satisfactory evidence) to be the person whose name is subscribed to the within instrument and acknowledged to me that he executed the same in his authorized capacity, and that by his signature on the instrument the person, or the entity upon behalf of which the person acted, executed the instrument.

I certify under PENALTY OF PERJURY under the laws of the State of _____ that the foregoing paragraph is true and correct.

WITNESS my hand and official seal.

_____
Signature (Seal)

WITNESSES TO SIGNATURE BY HAN HAN

1. Kaylale — Signature; April 6, 2016 — Date

KAYLA LE — Print Name

119 POPPY CT — Street Address

MILPITAS, CA 95035 — City, Country & Postal Code

2. J. Jason Lutes — Signature; 06 APR 2016 — Date

Jason Lutes — Print Name

263 Stanley Ave — Street Address

Pacifica, CA 94044 — City, Country & Postal Code

OR

STATE OF _____

COUNTY OF _____

On _____ before me, _____, personally appeared Han Han, personally known to me (or proved to me on the basis of satisfactory evidence) to be the person whose name is subscribed to the within instrument and acknowledged to me that she executed the same in her authorized capacity, and that by her signature on the instrument the person, or the entity upon behalf of which the person acted, executed the instrument.

I certify under PENALTY OF PERJURY under the laws of the State of _____ that the foregoing paragraph is true and correct.

WITNESS my hand and official seal.

_____
Signature (Seal)

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
18/408,486	01/09/2024		1064	092459-0422/8032.US05	30	3

CONFIRMATION NO. 5991

108547
McDermott Will & Emery LLP
500 North Capitol Street NW
Washington, DC 20001-1531

FILING RECEIPT

OC00000006738697

Date Mailed: 01/25/2024

Receipt is acknowledged of this non-provisional utility patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF FIRST INVENTOR, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection.

Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please submit a written request for a corrected Filing Receipt, including a properly marked-up ADS showing the changes with strike-through for deletions and underlining for additions. If you received a "Notice to File Missing Parts" or other Notice requiring a response for this application, please submit any request for correction to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections provided that the request is grantable.

Inventor(s)

Thomas B. Ottoboni, Belmont, CA;
Han Han, Sunnyvale, CA;

Applicant(s)

Heron Therapeutics, Inc., San Diego, CA;

Power of Attorney: The patent practitioners associated with Customer Number 108547

Domestic Priority data as claimed by applicant

This application is a CON of 18/535,853 12/11/2023
which is a CON of 17/180,593 02/19/2021 PAT 11,878,074
which is a CON of 16/820,311 03/16/2020 PAT 11,173,118
which is a CON of 15/965,638 04/27/2018 PAT 10,624,850
which is a CON of 15/012,532 02/01/2016 PAT 9,974,742

Foreign Applications for which priority is claimed (You may be eligible to benefit from the Patent Prosecution Highway program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 01/23/2024

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 18/408,486**

Projected Publication Date: 05/02/2024

Non-Publication Request: No

Early Publication Request: No
**** SMALL ENTITY ****
Title

METHODS OF USE OF EMULSION FORMULATIONS OF AN NK-1 RECEPTOR ANTAGONIST

Preliminary Class

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

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For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific

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Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

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NOT GRANTED

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Kathi Vidal

Kathi Vidal
Under Secretary of Commerce for Intellectual Property and
Director of the United States Patent and Trademark Office

Derrick Brent
Deputy Under Secretary of Commerce for Intellectual Property and
Deputy Director of the United States Patent and Trademark Office

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/408,486	01/09/2024	Thomas B. Ottoboni	092459-0422/8032.US05	5991

108547 7590 02/22/2024

McDermott Will & Emery LLP
500 North Capitol Street NW
Washington, DC 20001-1531

EXAMINER
CENTRAL, DOCKET

ART UNIT	PAPER NUMBER
OPAP	

NOTIFICATION DATE	DELIVERY MODE
02/22/2024	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ipdocketmwe@mwe.com

PTOL-90A (Rev. 04/07)

Decision Granting Request for Prioritized Examination (Track I)	**Application No.** 18/408,486	**Applicant(s)** Ottoboni et al.	
	Examiner CHERYL P GIBSON BAYLOR	**Art Unit** OPET	**AIA (FITF) Status** Yes

1. THE REQUEST FILED 09 January 2024 IS **GRANTED** .

   The above-identified application has met the requirements for prioritized examination
   - A. ☑ for an original nonprovisional application (Track I).
   - B. ☐ for an application undergoing continued examination (RCE).

2. **The above-identified application will undergo prioritized examination**. The application will be accorded special status throughout its entire course of prosecution until one of the following occurs:
   - A. filing a **petition for extension of time** to extend the time period for filing a reply;
   - B. filing an **amendment to amend the application to contain more than four independent claims, more than thirty total claims** , or a multiple dependent claim;
   - C. filing a **request for continued examination** ;
   - D. filing a notice of appeal;
   - E. filing a request for suspension of action;
   - F. mailing of a notice of allowance;
   - G. mailing of a final Office action;
   - H. completion of examination as defined in 37 CFR 41.102; or
   - I. abandonment of the application.

Telephone inquiries with regard to this decision should be directed to CHERYL GIBSON BAYLOR at (571)272-3213. In his/her absence, calls may be directed to Petition Help Desk at (571) 272-3282.

/CHERYL GIBSON BAYLOR/ Paralegal Specialist, OPET	

U.S. Patent and Trademark Office
PTO-2298 (Rev. 02-2012)

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/408,486	01/09/2024	Thomas B. Ottoboni	092459-0422/8032.US05	5991

108547 7590 03/26/2024

McDermott Will & Emery LLP
500 North Capitol Street NW
Washington, DC 20001-1531

EXAMINER
ABDALHAMEED, MANAHIL MIRGHANI ALI

ART UNIT	PAPER NUMBER
1622	

NOTIFICATION DATE	DELIVERY MODE
03/26/2024	ELECTRONIC

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PTOL-90A (Rev. 04/07)

Office Action Summary	**Application No.** 18/408,486	**Applicant(s)** Ottoboni et al.	
	Examiner MANAHIL M ABDALHAMEED	**Art Unit** 1622	**AIA (FITF) Status** Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 09 January 2024.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL.** 2b) ☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 1-30 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 1-30 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☑ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

DETAILED ACTION

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Priority

This application filed on 01/09/2024 is a continuation of U.S. Application No. 18/535,853, filed 12/11/2023, which is a continuation of U.S. Application No. 17/180,593, filed 02/19/2021 (now U.S. Patent No. 11878074), which is a continuation of U.S. Application No. 16/820,311, filed 03/16/2020 (now U.S. Patent No. 11,173,118), which is a continuation of U.S. Application No. 15/965,638, filed 04/27/2018 (now U.S. Patent No. 10,624,850), which is a continuation of U.S. Application No. 15/012,532, filed 02/01/2016 (now U.S. Patent No. 9,974,742).

DETAILED ACTION

Claims 1-30 are pending.

Claim objections

Claim 7 is objected to because of the following informalities:

Claim 7 recites "The emulsion of claim 5, wherein the **phospholipid** is present in the emulsion at about 17 wt/wt%." Claim 5 recites "The emulsion of claim 1, wherein the emulsifier is an **egg lecithin**." However, while claim 1 recites that the injectable emulsion comprises "an emulsifier", claim 1 perse does not define the emulsifier as phospholipid (dependent claims 2-4 define the emulsifier as phospholipid). While the egg lecithin Is known in the art as a phospholipid, it would be better if Applicant use consistent

claim dependency language. That is, claim 7 recite "wherein the egg lecithin" instead of "wherein the phospholipid" or change the dependency of claim 7.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP § 2146 *et seq.* for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b). The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should

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Double Patenting Rejection over US9561229B2

Claims 1-30 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-21 of U.S. Patent No. 9561229B2. Although the claims at issue are not identical, they are not patentably distinct from each other because:

The instant claims 1-30 recite an injectable pharmaceutical emulsion comprising 0.7-0.8wt% aprepitant, an emulsifier (phospholipid, egg lecithin); an oil (olive oil, soybean oil, etc.); a co-surfactant (ethanol); and water, wherein the ratio of the emulsifier to aprepitant ranges from about 20:1 to 25:1 (wt/wt %); and wherein the injectable emulsion further comprises an osmotic agent (sucrose); and pH modifier (sodium oleate).

US9561229B2 recited in claims 1-21 an injectable pharmaceutical emulsion comprising 0.4 wt/wt % to 1.0 wt/wt % aprepitant; 13 wt/wt % to 15 wt/wt % egg yolk lecithin; 9 wt/wt % to 10 wt/wt % soybean oil; and a pH modifier, wherein the pH modifier is sodium oleate; wherein the pH of the emulsion ranges from 7.5 to 9.0, wherein the emulsion comprises 0.7 wt/wt % aprepitant, wherein the emulsion comprises 14 wt/wt % egg yolk lecithin, wherein the emulsion further comprises 3 wt/wt % to 8 wt/wt % sucrose, wherein the emulsion further comprises 2 wt/wt % to 6 wt/wt % ethanol. The US9561229B2 ratio of egg yolk lecithin to aprepitant (calculates 1:15 to 1:32.5) overlaps with the range in present claim 1. Thus, the range recited in present claim 1 is obvious over the amount of emulsifier and aprepitant claimed in the

US9561229B2. Therefore, the conflicting claims 1-21 of US9561229B2 reads on the limitations of instant claims 1-30.

Double Patenting Rejection over US9808465B2

Claims 1-30 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-6, 8-9, 12-15 of U.S. Patent No. US9808465B2. Although the claims at issue are not identical, they are not patentably distinct from each other because:

The instant claims 1-30 recite an injectable pharmaceutical emulsion comprising 0.7-0.8wt% aprepitant, an emulsifier (phospholipid, egg lecithin); an oil (olive oil, soybean oil, etc.); a co-surfactant (ethanol); and water, wherein the ratio of the emulsifier to aprepitant ranges from about 20:1 to 25:1 (wt/wt %); and wherein the injectable emulsion further comprises an osmotic agent (sucrose); and pH modifier (sodium oleate).

US9808465B2 recited in claims 1-6, 8-9, 12-15, a composition comprising an injectable physically stable emulsion wherein the emulsion comprises aprepitant; 11 wt/wt % to 15 wt/wt % of an emulsifier; an oil; a co-emulsifier which is an alcohol; a tonicity modifier; a pH modifier; and water; wherein the ratio of emulsifier : aprepitant ranges from about 18:1 to 22:1, wherein the ratio of the oil to the aprepitant within the oil phase of the emulsion ranges from about 10:1 to 15:1 (wt/wt %), wherein the ethanol is less than 10 wt%, and wherein the emulsifier is an egg lecithin, wherein the pH modifier is sodium oleate, wherein the oil is soybean oil, wherein the alcohol in the emulsion is ethanol, and wherein the tonicity modifier in the emulsion is sucrose. The amount of aprepitant appears to be obvious considering the ratio between aprepitant to egg lecithin and 11-15% of egg lecithin (calculates to 0.6-0.8wt%). Therefore, the conflicting claims 1-6, 8-9, 12-15 of US9808465B2 reads on the limitations of instant claims 1-30.

Double Patenting Rejection over US9974742B2

Claims 1-30 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-6, 9, and 12-14 of U.S. Patent No. 9974742B2. Although the claims at issue are not identical, they are not patentably distinct from each other because:

The instant claims 1-30 recite an injectable pharmaceutical emulsion comprising 0.7-0.8wt% aprepitant, an emulsifier (phospholipid, egg lecithin); an oil (olive oil, soybean oil, etc.); a co-surfactant (ethanol); and water, wherein the ratio of the emulsifier to aprepitant ranges from about 20:1 to 25:1 (wt/wt %); and wherein the injectable emulsion further comprises an osmotic agent (sucrose); and pH modifier (sodium oleate).

US9974742B2 recited in claims 1-6, 9, and 12-14, an injectable pharmaceutical emulsion comprising a neurokinase-1 (NK-1) receptor antagonist; 11 wt/wt % to 15 wt/wt % of an emulsifier; an oil; a co-surfactant which comprises an alcohol; a tonicity agent; a pH modifier; and water, wherein the ratio of the emulsifier to the NK-1 receptor antagonist ranges from about 18:1 to 22:1 (wt/wt %), wherein the ratio of the oil to the NK-1 receptor antagonist ranges from about 5:1 to 15:1 (wt/wt %), wherein the emulsifier is an egg lecithin, wherein the pH modifier is oleic acid or a salt thereof, wherein the oil is soybean oil, wherein the alcohol is ethanol, wherein the ethanol is present in the emulsion at less than 10 wt/wt %. The amount of aprepitant appears to be obvious considering the ratio between aprepitant to egg lecithin and 11-15% of egg lecithin (calculates to 0.6-0.8wt%). Therefore, the conflicting claims 1-6, 9, and 12-14 of US9974742B2 reads on the limitations of instant claims 1-30.

Double Patenting Rejection over US9974793B2

Claims 1-30 are rejected on the ground of nonstatutory double patenting as being unpatentable over

claims 1-22 of U.S. Patent No. 9974793B2. Although the claims at issue are not identical, they are not patentably distinct from each other because:

The instant claims 1-30 recite an injectable pharmaceutical emulsion comprising 0.7-0.8wt% aprepitant, an emulsifier (phospholipid, egg lecithin); an oil (olive oil, soybean oil, etc.); a co-surfactant (ethanol); and water, wherein the ratio of the emulsifier to aprepitant ranges from about 20:1 to 25:1 (wt/wt %); and wherein the injectable emulsion further comprises an osmotic agent (sucrose); and pH modifier (sodium oleate).

US9974793B2 recited in claims 1-22, a physically stable pharmaceutical emulsion, comprising 0.4-1.0 wt/wt% aprepitant; an emulsifier (egg yolk lecithin); an oil (soybean oil); and water; wherein the ratio of the emulsifier to aprepitant (wt %:wt %) ranges from about 18:1 to 22:1, wherein the ratio of the oil to aprepitant (wt %:wt %) ranges from about 11:1 to 15:1, wherein the composition comprises 0.7 wt/wt % aprepitant; wherein the composition comprises 11 wt/wt % to 15 wt/wt % emulsifier; wherein the composition comprises 9 wt/wt % to 10 wt/wt % oil; wherein the composition further comprises sodium oleate as a pH modifier; wherein composition further comprises 3 wt/wt % to 8 wt/wt % sucrose; wherein the composition further comprises 6 wt/wt % ethanol. Therefore, the conflicting claims 1-22 of US9974793B2 meets the limitations of instant claims 1-30.

Double Patenting Rejection over US9974794B2

Claims 1-30 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-11 of U.S. Patent No. 9974794B2. Although the claims at issue are not identical, they are not patentably distinct from each other because:

The instant claims 1-30 recite an injectable pharmaceutical emulsion comprising 0.7-0.8wt% aprepitant, an emulsifier (phospholipid, egg lecithin); an oil (olive oil, soybean oil, etc.); a co-surfactant (ethanol); and water, wherein the ratio of the emulsifier to aprepitant ranges from about 20:1 to 25:1 (wt/wt %); and wherein the injectable emulsion further comprises an osmotic agent (sucrose); and pH modifier (sodium oleate).

US9974794B2 recited in claims 1-11, a physically stable emulsion pharmaceutical composition, comprising 0.4-1.0 wt/wt% aprepitant; 13-15 wt/wt% egg yolk lecithin); 9-10 wt/wt% soybean oil; sodium oleate as a pH modifier; wherein the ratio of the emulsifier to aprepitant (wt %:wt %) ranges from about 18:1 to 22:1, wherein the composition comprises 0.7 wt/wt % aprepitant; wherein the composition comprises 9 wt/wt % to 10 wt/wt % oil; wherein the composition further comprises wherein composition further comprises 3 wt/wt % to 8 wt/wt % sucrose; wherein the composition further comprises 6 wt/wt % ethanol. Therefore, the conflicting claims 1-11 of US9974794B2 meets the limitations of instant claims 1-30.

Double Patenting Rejection over US10500208B2

Claims 1-30 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-5, 7-9, 11-13 of U.S. Patent No. 10500208B2. Although the claims at issue are not identical, they are not patentably distinct from each other because:

The instant claims 1-30 recite an injectable pharmaceutical emulsion comprising 0.7-0.8wt% aprepitant, an emulsifier (phospholipid, egg lecithin); an oil (olive oil, soybean oil, etc.); a co-surfactant (ethanol); and water, wherein the ratio of the emulsifier to aprepitant ranges from about 20:1 to 25:1 (wt/wt %); and wherein the injectable emulsion further comprises an osmotic agent (sucrose); and pH

modifier (sodium oleate).

US10500208B2 recited in claims 1-5, 7-9, and 11-13, an injectable emulsion comprising aprepitant; 11 wt/wt % to 15 wt/wt % of an emulsifier; an oil; a co emulsifier which is an alcohol; a tonicity modifier; a pH modifier; and water; wherein the ratio of the emulsifier to the aprepitant in the emulsion ranges from about 15:1 to 30:1 (wt/wt %), wherein the ratio of the oil to the aprepitant in the emulsion ranges from about 11:1 to 15:1 (wt/wt %), wherein the emulsifier is an egg lecithin, wherein the pH modifier is sodium oleate, wherein the oil is soybean oil, wherein the alcohol is less than 10 wt/wt % ethanol. The amount of aprepitant appears to be obvious considering the ratio between aprepitant to egg lecithin and 11-15% of egg lecithin (calculates to 0.7-1.0wt%). Therefore, the conflicting claims 1-5, 7-9, and 11-13 of US10500208B2 reads on the limitations of instant claims 1-30.

Double Patenting Rejection over US10624850B2

Claims 1-30 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-6, 9, and 12-16 of U.S. Patent No. 10624850B2. Although the claims at issue are not identical, they are not patentably distinct from each other because:

The instant claims 1-30 recite an injectable pharmaceutical emulsion comprising 0.7-0.8wt% aprepitant, an emulsifier (phospholipid, egg lecithin); an oil (olive oil, soybean oil, etc.); a co-surfactant (ethanol); and water, wherein the ratio of the emulsifier to aprepitant ranges from about 20:1 to 25:1 (wt/wt %); and wherein the injectable emulsion further comprises an osmotic agent (sucrose); and pH modifier (sodium oleate).

US10624850B2 recited in claims 1-6, 9, and 12-16 an injectable pharmaceutical emulsion,

wherein the emulsion comprises a neurokinase-1 (NK-1) receptor antagonist; 11 wt/wt % to 15 wt/wt % of an emulsifier (egg lecithin); an oil (soybean oil); a co-surfactant which comprises less than 10 wt/wt % ethanol; a tonicity agent; a pH modifier (oleic acid or a salt thereof); and water, wherein the ratio of the emulsifier to the NK-1 receptor antagonist ranges from about 18:1 to 22:1 (wt/wt %), wherein the ratio of the oil to the NK-1 receptor antagonist ranges from about 5:1 to 15:1 (wt/wt %). The instant specification defined aprepitant as NK-1 receptor antagonist. The amount of aprepitant appears to be obvious considering the ratio between aprepitant to egg lecithin and 11-15% of egg lecithin (calculates to 0.6-0.8wt%). Therefore, the conflicting claims 1-6, 9, and 12-16 of US10624850B2 reads on the limitations of instant claims 1-30.

Double Patenting Rejection over US10953018B2

Claims 1-30 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-18 of U.S. Patent No. 10953018B2. Although the claims at issue are not identical, they are not patentably distinct from each other because:

The instant claims 1-30 recite an injectable pharmaceutical emulsion comprising 0.7-0.8wt% aprepitant, an emulsifier (phospholipid, egg lecithin); an oil (olive oil, soybean oil, etc.); a co-surfactant (ethanol); and water, wherein the ratio of the emulsifier to aprepitant ranges from about 20:1 to 25:1 (wt/wt %); and wherein the injectable emulsion further comprises an osmotic agent (sucrose); and pH modifier (sodium oleate).

US10953018B2 recited in claims 1-18, a physically stable pharmaceutical emulsion, comprising 0.4-1.0 wt/wt% aprepitant; an emulsifier (11-15 wt/wt% egg yolk lecithin); an oil (9-10 wt/wt% soybean oil); and water; wherein the ratio of the emulsifier to aprepitant (wt %:wt %) ranges from about 18:1 to

22:1; wherein the composition comprises 0.7 wt/wt % aprepitant; wherein the composition further comprises sodium oleate as a pH modifier; wherein the composition further comprises 3 wt/wt % to 8 wt/wt % sucrose. Therefore, the conflicting claims 1-18 of US10953018B2 meets the limitations of instant claims 1-30.

Double Patenting Rejection over US11173118B2

Claims 1-30 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-8, 11-12, and 14-17 of U.S. Patent No. 11173118B2. Although the claims at issue are not identical, they are not patentably distinct from each other because:

The instant claims 1-30 recite an injectable pharmaceutical emulsion comprising 0.7-0.8wt% aprepitant, an emulsifier (phospholipid, egg lecithin); an oil (olive oil, soybean oil, etc.); a co-surfactant (ethanol); and water, wherein the ratio of the emulsifier to aprepitant ranges from about 20:1 to 25:1 (wt/wt %); and wherein the injectable emulsion further comprises an osmotic agent (sucrose); and pH modifier (sodium oleate).

US11173118B2 recited in claims 1-8, 11-12, and 14-17, an injectable pharmaceutical emulsion comprising, a neurokinase-1 (NK-1) receptor antagonist; an emulsifier (egg lecithin); an oil (soybean oil); a co-surfactant (ethanol); and an aqueous phase; wherein the ratio of the emulsifier to the NK-1 receptor antagonist ranges from about 18:1 to 22:1 (wt/wt %); wherein the ratio of the oil to the NK-1 receptor antagonist ranges from about 5:1 to 15:1 (wt/wt %); wherein the aqueous phase comprises water and a tonicity agent and a pH modifying agent (oleate or a salt thereof). Therefore, the conflicting claims 1-8, 11-12, and 14-17 of US11173118B2 meets the limitations of instant claims 1-30.

Double Patenting Rejection over US11744800B2

Claims 1-30 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-21 of U.S. Patent No. 11744800B2. Although the claims at issue are not identical, they are not patentably distinct from each other because:

The instant claims 1-30 recite an injectable pharmaceutical emulsion comprising 0.7-0.8wt% aprepitant, an emulsifier (phospholipid, egg lecithin); an oil (olive oil, soybean oil, etc.); a co-surfactant (ethanol); and water, wherein the ratio of the emulsifier to aprepitant ranges from about 20:1 to 25:1 (wt/wt %); and wherein the injectable emulsion further comprises an osmotic agent (sucrose); and pH modifier (sodium oleate).

US11744800B2 recited in claims 1-21 an injectable pharmaceutical emulsion comprising aprepitant, about 14-15 wt/wt % egg lecithin (an emulsifier, phospholipid); about 9-10 wt/wt % soybean oil (an oil); about 3 wt/wt% ethanol (a co-surfactant); about 3-8 wt/wt % sucrose (an osmotic agent); sodium oleate (a pH modifier); and water, wherein the ratio of the egg lecithin to aprepitant ranges from about 18:1 to 22:1 (wt/wt %). The amount of aprepitant appears to be met considering the ratio between aprepitant to egg lecithin and 14-15% of egg lecithin (calculates to 0.78-0.8wt%). Therefore, the conflicting claims 1-21 of US11744800B2 meets the limitations of instant claims 1-30.

Double Patenting Rejection over US11878074B2

Claims 1-30 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-21 of U.S. Patent No. 11878074B2. Although the claims at issue are not identical, they are not patentably distinct from each other because:

The instant claims 1-30 recite an injectable pharmaceutical emulsion comprising 0.7-0.8wt% aprepitant, an emulsifier (phospholipid, egg lecithin); an oil (olive oil, soybean oil, etc.); a co-surfactant (ethanol); and water, wherein the ratio of the emulsifier to aprepitant ranges from about 20:1 to 25:1 (wt/wt %); and wherein the injectable emulsion further comprises an osmotic agent (sucrose); and pH modifier (sodium oleate).

11878074B2 recites in claims 1-5, 7-9, and 11-14, an injectable pharmaceutical emulsion comprising: aprepitant; an emulsifier; an oil; a co-surfactant; and an aqueous phase, wherein the ratio of the emulsifier to the NK-1 receptor antagonist ranges from about 18:1 to 22:1 (wt/wt%); wherein the ratio of the oil to the NK-1 receptor antagonist ranges from about 5:1 to 15:1 (wt/wt%); wherein the emulsion comprises between about 11 wt/wt% to 15 wt/wt% of an emulsifier; wherein the emulsifier is a phospholipid; wherein the pH modifier is oleic acid or a salt thereof; wherein the oil is soybean oil; the alcohol is ethanol. The amount of aprepitant appears to be obvious considering the ratio between aprepitant to egg lecithin and 11-15% of egg lecithin (calculates to 0.6-0.8wt%). Therefore, the conflicting claims 1-5, 7-9, and 11-14 of 11878074B2 reads on the limitations of instant claims 1-30.

Double Patenting Rejection over U.S. co-pending Application No. 17/194,114

Claims 1-30 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-19, 21-28 of co-pending Application No. 17/194,114 (US20210186981A1). Although the claims at issue are not identical, they are not patentably distinct from each other because:

The instant claims 1-30 recite an injectable pharmaceutical emulsion comprising 0.7-0.8wt% aprepitant, an emulsifier (phospholipid, egg lecithin); an oil (olive oil, soybean oil, etc.); a co-surfactant (ethanol); and water, wherein the ratio of the emulsifier to aprepitant ranges from about 20:1 to 25:1

(wt/wt %); and wherein the injectable emulsion further comprises an osmotic agent (sucrose); and pH modifier (sodium oleate).

Co-pending Application No. 17/194,114 recites in claims 1-19 and 21-28, a physically stable pharmaceutical emulsion comprising aprepitant; an emulsifier; an oil; and water; wherein the ratio of the emulsifier to aprepitant (wt %:wt %) ranges from about 18:1 to 22:1, wherein the composition comprises 11-15 wt/wt % emulsifier; wherein the emulsifier is egg yolk lecithin; wherein the composition comprises 9 -10 wt/wt % oil; wherein the oil is soybean oil; wherein the composition further comprises sodium oleate as a pH modifier; wherein the composition further comprises 3-8 wt/wt % sucrose; wherein the composition further comprises 6 wt/wt % ethanol. The claimed amount of aprepitant appears to be obvious considering the ratio between aprepitant to egg lecithin and 11-15% of egg lecithin (calculates to 0.6-0.8wt%). Therefore, the conflicting claims 1-19 and 21-28 of co-pending Application No. 17/194,114 reads on the limitations of instant claims 1-30. This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Double Patenting Rejection over U.S. co-pending Application No. 16/261,459

Claims 1-30 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 31, 39-46, 51, 54-62 and 65-71 of co-pending Application No. 16/261,459 (US20190231688A1). Although the claims at issue are not identical, they are not patentably distinct from each other because:

The instant claims 1-30 recite an injectable pharmaceutical emulsion comprising 0.7-0.8wt% aprepitant, an emulsifier (phospholipid, egg lecithin); an oil (olive oil, soybean oil, etc.); a co-surfactant (ethanol); and water, wherein the ratio of the emulsifier to aprepitant ranges from about 20:1 to 25:1

(wt/wt %); and wherein the injectable emulsion further comprises an osmotic agent (sucrose); and pH modifier (sodium oleate).

Co-pending Application No. 16/261,459 recites in claims 31, 39-46, 51, 54-62 and 65-71, an emulsion comprising 100-200 mg of aprepitant; 10-20 wt/wt% of an emulsifier; an oil; less than 10 wt/wt% ethanol; a tonicity agent; a pH modifier and water; wherein the ratio of the emulsifier to aprepitant (wt %:wt %) ranges from about 20:1 to 25:1, wherein the ratio of the oil to the aprepitant ranges from about 10:1 to 15:1 wt/wt%; wherein the emulsifier is 17 wt/wt % of phospholipid egg lecithin; wherein the oil is soybean oil; wherein the pH modifier sodium is oleate. The claimed amount of aprepitant, 0.7-0.8wt% appears to be obvious considering the amount of aprepitant and emulsifier recited in claims 45 (calculates to 0.5:1 to 0.4:0.8). Therefore, the conflicting claims 31, 39-46, 51, 54-62 and 65-71 of co-pending Application No. 16/261,459 reads on the limitations of instant claims 1-30.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Double Patenting Rejection over U.S. co-pending Application No. 18/408,463

Claims 1-30 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-28 of co-pending Application No. 18/408,463 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because:

The instant claims 1-30 recite an injectable pharmaceutical emulsion comprising 0.7-0.8wt% aprepitant, an emulsifier (phospholipid, egg lecithin); an oil (olive oil, soybean oil, etc.); a co-surfactant (ethanol); and water, wherein the ratio of the emulsifier to aprepitant ranges from about 20:1 to 25:1 (wt/wt %); and wherein the injectable emulsion further comprises an osmotic agent (sucrose); and pH

modifier (sodium oleate).

Co-pending Application No. 18/408,463 recites in claims 1-28, an injectable emulsion comprising aprepitant; 13-20 wt/wt% of an emulsifier (17 wt/wt% egg lecithin); an 9-10 wt/wt% oil (soybean oil); co-emulsifier (less than 10 wt/wt% ethanol); a tonicity modifier (3-8 wt/wt% sucrose); a pH modifier (sodium oleate); and water; wherein the ratio of the emulsifier to aprepitant (wt %:wt %) ranges from about 20:1 to 25:1. The claimed amount of aprepitant appears to be obvious considering the ratio between aprepitant to egg lecithin and 13-20% of egg lecithin (calculates to 0.65-0.8wt%).Therefore, the conflicting claims 1-19 and 21-28 of co-pending Application No. 17/194,114 reads on the limitations of instant claims 1-30. This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Double Patenting Rejection over U.S. co-pending Application No. 18/418,030

Claims 1-30 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claim claims 1-30 of co-pending Application No. 18/418,030 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because:

The instant claims 1-30 recite an injectable pharmaceutical emulsion comprising 0.7-0.8wt% aprepitant, an emulsifier (phospholipid, egg lecithin); an oil (olive oil, soybean oil, etc.); a co-surfactant (ethanol); and water, wherein the ratio of the emulsifier to aprepitant ranges from about 20:1 to 25:1 (wt/wt %); and wherein the injectable emulsion further comprises an osmotic agent (sucrose); and pH modifier (sodium oleate).

Co-pending Application No. 18/418,030 recites in claims 1-30, an injectable emulsion comprising

0.7-0.8 wt/wt% aprepitant; 13-20 wt/wt% of an emulsifier (17 wt/wt% egg lecithin); an 9-10 wt/wt% oil (soybean oil); co-emulsifier (less than 10 wt/wt% ethanol); a tonicity modifier (3-8 wt/wt% sucrose); a pH modifier (sodium oleate); and water; wherein the ratio of the emulsifier to aprepitant (wt %:wt %) ranges from about 20:1 to 25:1. Therefore, the conflicting claims 1-30 of co-pending Application No. 18/418,030 meets the limitations of instant claims 1-30.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Double Patenting Rejection over U.S. co-pending Application No. 18/535,853

Claims 1-30 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-20 of co-pending Application No. 18/535,853 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because:

The instant claims 1-30 recite an injectable pharmaceutical emulsion comprising 0.7-0.8wt% aprepitant, an emulsifier (phospholipid, egg lecithin); an oil (olive oil, soybean oil, etc.); a co-surfactant (ethanol); and water, wherein the ratio of the emulsifier to aprepitant ranges from about 20:1 to 25:1 (wt/wt %); and wherein the injectable emulsion further comprises an osmotic agent (sucrose); and pH modifier (sodium oleate).

Co-pending Application No. 18/535,853 recites in claims 1-20, an injectable emulsion comprising 0.7-0.8 wt/wt% aprepitant; 11-15 wt/wt% of an emulsifier (egg lecithin); an 9-10 wt/wt% oil (soybean oil); co-emulsifier (6 wt/wt% ethanol); a tonicity modifier (3-8 wt/wt% sucrose); a pH modifier (sodium oleate); and water; wherein the ratio of the emulsifier to aprepitant (wt %:wt %) ranges from about 18:1 to 22:1. Therefore, the conflicting claims 1-20 of co-pending Application No. 18/535,853 meets the

limitations of instant claims 1-30.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MANAHIL MIRGHANI ALI ABDALHAMEED whose telephone number is (571)272-1242. The examiner can normally be reached M-F 7:30 am - 5:00 pm.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Havlin can be reached on 571-272-9066. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/M.M.A./
Examiner, Art Unit 1622

/BAHAR CRAIGO/
Primary Examiner, Art Unit 1699

Notice of References Cited	Application/Control No. 18/408,486	Applicant(s)/Patent Under Reexamination Ottoboni et al.	
	Examiner MANAHIL M ABDALHAMEED	Art Unit 1622	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date YYYY-MM-DD	Name	CPC Classification	US Classification
*	A	US-9561229-B2	2017-02-07	Ottoboni; Thomas B.	A61K47/24	1/1
*	B	US-9808465-B2	2017-11-07	Ottoboni; Thomas B.	A61K47/12	1/1
*	C	US-9974742-B2	2018-05-22	Ottoboni; Thomas B.	A61K9/1075	1/1
*	D	US-9974793-B2	2018-05-22	Ottoboni; Thomas B.	A61K47/24	1/1
*	E	US-9974794-B2	2018-05-22	Ottoboni; Thomas B.	A61K9/0024	1/1
*	F	US-10500208-B2	2019-12-10	Ottoboni; Thomas B.	A61P43/00	1/1
*	G	US-10624850-B2	2020-04-21	Ottoboni; Thomas B.	A61K31/435	1/1
*	H	US-10953018-B2	2021-03-23	Ottoboni; Thomas B.	A61K47/44	1/1
*	I	US-11173118-B2	2021-11-16	Ottoboni; Thomas B.	A61K31/43	1/1
*	J	US-11744800-B2	2023-09-05	Ottoboni; Thomas B.	A61K31/573	707/750
*	K	US-11878074-B2	2024-01-23	Ottoboni; Thomas B.	A61K31/435	1/1
*	L	US-20210186981-A1	2021-06-24	Ottoboni; Thomas B.	A61P1/08	1/1
*	M	US-20190231688-A1	2019-08-01	Ottoboni; Thomas B.	A61K47/12	1/1

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date YYYY-MM-DD	Country	Name	CPC Classification
	N					
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*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: THOMAS B. OTTOBONI	EXAMINER: ABDALHAMEED, MANAHIL MIRGHANI ALI
APPLICATION NO.: 18/408,486	ART UNIT: 1622
FILED: JANUARY 9, 2024	CONF. NO: 5991
FOR: METHODS OF USE OF EMULSION FORMULATIONS OF AN NK-1 RECEPTOR ANTAGONIST	

Amendment Under 37 C.F.R. § 1.111

Mail Stop: Amendment
Commissioner for Patents
U.S. Patent & Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

The present communication responds to the Office Action dated March 26, 2024 in the above-identified application.

Please amend the application as follows:

Amendments to the Claims are reflected in the listing of claims beginning on page 2.

Remarks begin on page 5.

[The remainder of this page is intentionally left blank.]

Amendments to the Claims

The following Listing of Claims, in which deleted text appears ~~struck through~~ or [[double-bracketed]] and inserted text appears underlined, will replace all prior versions, and listings, of claims in the application.

1. (Original) An injectable pharmaceutical emulsion, comprising:
about 0.7-0.8 wt% aprepitant;
an emulsifier;
an oil;
a co-surfactant; and
water,
wherein the ratio of the emulsifier to aprepitant ranges from about 20:1 to 25:1 (wt/wt%).

2. (Original) The emulsion of claim 1, wherein the emulsifier is a phospholipid.

3. (Original) The emulsion of claim 2, wherein the phospholipid is present in the emulsion at about 16 wt/wt%.

4. (Original) The emulsion of claim 2, wherein the phospholipid is present in the emulsion at about 17 wt/wt%.

5. (Original) The emulsion of claim 1, wherein the emulsifier is an egg lecithin.

6. (Original) The emulsion of claim 5, wherein the egg lecithin is present in the emulsion at about 16 wt/wt%.

7. (Currently amended) The emulsion of claim 5, wherein the egg lecithin ~~phospholipid~~ is present in the emulsion at about 17 wt/wt%.

8. (Original) The emulsion of claim 1, wherein the oil is selected from the group consisting of coconut oil, olive oil, soybean oil, safflower oil, triglycerides, octyl and decyl glycerate, ethyl oleate, glyceryl linoleate, ethyl linoleate, glyceryl oleate, cholesteryl oleate, cholesteryl linoleate, and mixtures thereof.

9. (Original) The emulsion of claim 8, wherein the oil is present at a concentration of about 9 wt/wt % to 10 wt/wt %.

10. (Original) The emulsion of claim 1, wherein the co-surfactant comprises an alcohol.

11. (Original) The emulsion of claim 10, wherein the alcohol is present in the emulsion at less than 10 wt/wt%.

12. (Original) The emulsion of claim 10, wherein the co-surfactant is ethanol.

13. (Original) The emulsion of claim 1, further comprising an osmotic agent.

14. (Original) The emulsion of claim 13, wherein the osmotic agent is selected from the group consisting of glycerol, sorbitol, xylitol, mannitol, glucose, trehalose, maltose, sucrose, raffinose, lactose, dextran, polyethylene glycol, or propylene glycol.

15. (Original) The emulsion of claim 14, wherein the osmotic agent is present at a concentration of about 3 wt/wt % to 8 wt/wt %.

16. (Original) The emulsion of claim 1, further comprising a pH modifier.

17. (Original) The emulsion of claim 16, wherein the pH modifier is oleic acid or a salt thereof.

18. (Original) The emulsion of claim 1, wherein the emulsifier is egg lecithin.

19. (Original) The emulsion of claim 1, wherein the co-surfactant is ethanol.

20. (Original) The emulsion of claim 1, further comprising sucrose.

21. (Original) The emulsion of claim 1, further comprising sodium oleate

22. (Original) An injectable pharmaceutical emulsion, comprising:
about 0.7-0.8 wt% aprepitant;
an emulsifier;
an oil;

a co-surfactant; and

water,

wherein the ratio of the emulsifier to aprepitant ranges about 23:1 (wt/wt%).

23. (Original) The emulsion of claim 22, wherein the emulsifier is a phospholipid.

24. (Original) The emulsion of claim 23, wherein the phospholipid is selected from the group consisting of egg phospholipids and soy phospholipids.

25. (Original) The emulsion of claim 22, wherein the oil is selected from the group consisting of coconut oil, olive oil, soybean oil, safflower oil, triglycerides, octyl and decyl glycerate, ethyl oleate, glyceryl linoleate, ethyl linoleate, glyceryl oleate, cholesteryl oleate, cholesteryl linoleate, and mixtures thereof.

26. (Original) The emulsion of claim 22, wherein the co-surfactant comprises an alcohol present in the emulsion at less than 10 wt/wt%.

27. (Original) An injectable pharmaceutical emulsion, comprising:

about 0.7-0.8 wt% aprepitant;

an emulsifier;

an oil;

a co-surfactant; and

water,

wherein the ratio of the emulsifier to aprepitant ranges about 24:1 (wt/wt%).

28. (Original) The emulsion of claim 27, wherein the emulsifier is a phospholipid.

29. (Original) The emulsion of claim 27, wherein the phospholipid is selected from the group consisting of egg phospholipids and soy phospholipids.

30. (Original) The emulsion of claim 27, wherein the oil is selected from the group consisting of coconut oil, olive oil, soybean oil, safflower oil, triglycerides, octyl and decyl glycerate, ethyl oleate, glyceryl linoleate, ethyl linoleate, glyceryl oleate, cholesteryl oleate, cholesteryl linoleate, and mixtures thereof.

REMARKS

Reconsideration and withdrawal of the rejections set forth in the Office Action dated March 26, 2024 are respectfully requested.

I. Claim Amendment

Claim 7 is amended to address the objection in the Office Action. In accordance with the Examiner's suggestion, claim 7 has been amended to substitute "phospholipid" with "egg lecithin."

II. Obviousness Type Double-Patenting Rejections

The proffered nonstatutory double patenting rejections are grouped below according to Applicant's response.

GROUP 1: REJECTIONS ADDRESSED BY FILING A TERMINAL DISCLAIMER

Claims 1-30 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-21 of U.S. Patent No. 9,561,229.

Claims 1-30 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-6, 8-9, and 12-15 of U.S. Patent No. 9,808,465.

Claims 1-30 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-6, 9, and 12-14 of U.S. Patent No. 9,974,742.

Claims 1-30 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-22 of U.S. Patent No. 9,974,793.

Claims 1-30 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-11 of U.S. Patent No. 9,974,794.

Claims 1-30 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-5, 7-9, and 11-13 of U.S. Patent No. 10,500,208.

Claims 1-30 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-6, 9, and 12-16 of U.S. Patent No. 10,624,850.

Claims 1-30 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-18 of U.S. Patent No. 10,953,018.

Claims 1-30 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-8, 11-12, and 14-17 of U.S. Patent No. 11,173,118.

Claims 1-30 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-21 of U.S. Patent No. 11,744,800.

Claims 1-30 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-21 of U.S. Patent No. 11,878,074.

Claims 1-30 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-28 of co-pending Application No. 18/408,463.

Claims 1-30 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claim claims 1-30 of co-pending Application No. 18/418,030.

Claims 1-30 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-20 of co-pending Application No. 18/535,853.

Without conceding to the validity of these rejections, Applicant herewith submits an executed terminal disclaimer filed in accordance with C.F.R. §1.321(b) and (c) which disclaims the terminal portion of any Patent issuing on the instant application that extends beyond the expiration of U.S. Patent Nos.: 9,561,229; 9,808,465; 9,974,742; 9,974,793; 9,974,794; 10,500,208; 10,624,850; 10,953,018; 11,173,118; 11,744,800; and 11,878,074; and beyond the expiration of any patent that issues from, 18/408,463, 18/418,030, and 18/535,853. Withdrawal of the nonstatutory double patenting rejections is respectfully requested.

GROUP 2: REJECTION OVER A NOW ABANDONED APPLICATION

Claims 1-30 were provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-19 and 21-28 of co-pending Application No. 17/194,114.

Application No. 17/194,114 is abandoned. A Notice of Abandonment was mailed by the USPTO on March 7, 2024. Withdrawal of the rejection is respectfully requested.

GROUP 3: REJECTION OVER A LATER-FILED APPLICATION

Claims 1-30 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 31, 39-46, 51, 54-62, and 65-71 of co-pending Application No. 16/261,459.

Reconsideration and withdrawal is requested. The instant application has a patent term filing date of February 1, 2016. Application No. 16/261,459 has a patent term filing date of January 29, 2019, and is therefore later filed than the instant application. In accord with M.P.E.P.

§ 804, and in view of the terminal disclaimer filed herewith to resolve the other rejections, the nontstatutory double patenting rejection over Application No. 16/261,459 is the only remaining rejection. Since the instant case has an earlier patent term filing date the rejection should be withdrawn. (*See,* M.P.E.P. § 804 (I)(B)(1)(b)(i) "If a provisional nonstatutory double patenting rejection is the only rejection remaining in an application having the earlier patent term filing date, the examiner should withdraw the rejection in the application having the earlier patent term filing date and permit that application to issue as a patent, thereby converting the provisional nonstatutory double patenting rejection in the other application into a nonstatutory double patenting rejection upon issuance of the patent.").

III. Conclusion

The Commissioner is hereby authorized and requested to charge any deficiency in fees herein to Deposit Account No. **50-0417**.

In view of the foregoing, the claims are in condition for allowance. A Notice of Allowance is, therefore, respectfully requested. If the Examiner has any questions or believes a telephone conference would expedite prosecution of this application, the Examiner is encouraged to call the undersigned at (650) 815-7630.

Respectfully submitted,
MCDERMOTT WILL & EMERY LLP

Date: May 24, 2024

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PATENT AND TRADEMARK OFFICE

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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/408,486	**05/24/2024 05:49:12 PM Z ET**	**092459-0422/8032.US05**

Title of Invention

METHODS OF USE OF EMULSION FORMULATIONS OF AN NK-1 RECEPTOR ANTAGONIST

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	5991	FILED BY	Judy Steinkraus
PATENT CENTER #	65666173	FILING DATE	01/09/2024
CUSTOMER #	108547	FIRST NAMED INVENTOR	Thomas B. Ottoboni
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Judy Mohr

Documents

TOTAL DOCUMENTS: 37

DOCUMENT		PAGES	DESCRIPTION	SIZE (KB)
Response.pdf		7	-	43 KB
Response-A....pdf	(1-1)	1	Amendment/Request for Reconsideration-After Non-Final Rejection	22 KB
Response-CLM.pdf	(2-4)	3	Claims	22 KB
Response-REM.pdf	(5-7)	3	Applicant Arguments/Remarks Made in an Amendment	30 KB
Aziz2012AnnPalliatMed130to136.pdf		7	Non Patent Literature	220 KB

Cassileth1983ArchInternMed 1347to1349AbstOnly.pdf	3	Non Patent Literature	224 KB
cn103520725EngMachTrans.pdf	25	Foreign Reference	3242 KB
cn102379845EngTrans.pdf	17	Foreign Reference	3392 KB
Curran2009Drugs1853to1878.pdf	26	Non Patent Literature	5344 KB
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DexamethasoneSodiumPhosphate2017Drugs21pgs.pdf	21	Non Patent Literature	2219 KB
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Lipiod2018ProductFinderHome2pgs.pdf	2	Non Patent Literature	39 KB
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Navari1999NEngJMed190to195.pdf	6	Non Patent Literature	115 KB
jp1113315.pdf	6	Foreign Reference	1390 KB
jp2005225818.pdf	11	Foreign Reference	4067 KB

PharmCompLab2016EmulsionPrepStab1pg.pdf	1	Non Patent Literature	25 KB
Sun2013CancerChemPharm509to513.pdf	5	Non Patent Literature	470 KB
Ottoboni2016Declaration9pgs.pdf	9	Other reference-Patent/Application/Search Documents	434 KB
Takahashi2011CancerChemotherPharmacol653to659.pdf	7	Non Patent Literature	752 KB
Takagi2005FragranceJ131to138.pdf	8	Non Patent Literature	1308 KB
US15083071InterviewSummary4pgs.pdf	4	Other reference-Patent/Application/Search Documents	215 KB
Weng2012EurJLipidSciTechnol1154to1164.pdf	11	Non Patent Literature	1608 KB
wo2009124756.pdf	71	Foreign Reference	3258 KB
wo2005016308.pdf	57	Foreign Reference	3522 KB
wo2013177501.pdf	20	Foreign Reference	1258 KB
wo2011158053.pdf	22	Foreign Reference	1359 KB
wo2014005606.pdf	24	Foreign Reference	1988 KB
wo2014209962.pdf	63	Foreign Reference	3604 KB
wo2013101749.pdf	79	Foreign Reference	3934 KB
Zhou2012ChineseJPharm1003to1006EnglishTransOnly.pdf	4	Non Patent Literature	423 KB

wo2017135923.pdf	49	Foreign Reference	2663 KB
wo2016044784.pdf	36	Foreign Reference	2770 KB
IDS_Transmittal.pdf	2	Transmittal Letter	31 KB
IDS_SB08___.pdf	4	Information Disclosure Statement (IDS) Form (SB08)	54 KB

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Digest

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This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Attorney Docket No. 092459-0422/8032.US05

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Examiner:
Thomas B. OTTOBONI *et al.*	Manahil Mirghani Ali ABDALHAMEED
Application No.: 18/408,486	Art Unit: 1622
Filed: January 9, 2024	Conf. No.: 5991
For: **METHODS OF USE OF EMULSION FORMULATIONS OF AN NK-1 RECEPTOR ANTAGONIST**	

Information Disclosure Statement after First Office Action but Before Final Action or Notice of Allowance 37 CFR 1.97(c)

Mail Stop Amendment
Commissioner for Patents
U.S. Patent & Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

A. Timing of Submission

The information transmitted herewith is being filed *after* three months of the filing date of this application or after the mailing date of the first Office action on the merits, whichever occurred last, but *before* the mailing date of either a final action under 37 C.F.R. § 1.113 or a Notice of Allowance under 37 C.F.R. §1.311, whichever occurs first. The references listed on the enclosed Form PTO-1449 (modified) may be material to the examination of this application; the Examiner is requested to make them of record in the application.

B. Cited References

☒ Copies of cited references 1-31 which are issued patent(s) and/or published application(s) are not included (see 37 C.F.R. § 1.98(a) (2)(ii)).

☒ Copies of cited references 32-63 are enclosed.

C. Effect of Information Disclosure Statement (37 C.F.R. § 1.97(h))

This Information Disclosure Statement is not to be construed as a representation that: (i) a search has been made; (ii) additional information material to the examination of this application does not exist; (iii) the information, protocols,

results and the like reported by third parties are accurate or enabling; or (iv) the cited information is, or is considered to be, material to patentability. In addition, applicant does not admit that any enclosed item of information constitutes prior art to the subject invention and specifically reserves the right to demonstrate that any such reference is not prior art.

D. Fee Payment (37 C.F.R. § 1.97(c)) or Certification (37 C.F.R. § 1.97(e))

☒ Applicant elects to pay the fee under 37 CFR § 1.17(p) in the amount of $260.00.

☒ Applicant asserts small entity status under 37 CFR § 1.27. Fees above are reduced by 60%.

☐ Applicant asserts micro entity status under 37 CFR § 1.29. Fees above are reduced by 80%.

☒ Please charge Deposit Account No. 50-0417 in the amount of $104.00.

☒ The Commissioner is hereby authorized to charge any deficiency in fees to ensure timely submission of these papers to Deposit Account No. 50-0417.

E. Patent Term Adjustment (37 C.F.R. § 1.704(d))

☐ The undersigned states that each item of information submitted herewith was cited in a communication from a foreign patent office in a counterpart application and that this communication was not received by any individual designated in 37 C.F.R. § 1.56(c) more than thirty days prior to the filing of this statement. 37 C.F.R. § 1.704(d).

Respectfully submitted,
McDermott Will & Emery LLP

Date: May 24, 2024

/Judy Mohr/
Judy Mohr
Registration No. 38,563

Correspondence Address:
Customer No. 108547

INFORMATION DISCLOSURE STATEMENT BY APPLICANT Form PTO-1449 (Modified) (Use several sheets if necessary)				***COMPLETE IF KNOWN***	
				Application Number	18/408,486
				Confirmation Number	5991
				Filing Date	January 9, 2024
				First Named Inventor	Thomas B. OTTOBONI
				Group Art Unit	1622
				Examiner Name	Manahil Mirghani Ali ABDALHAMEED
Sheet	1	of	4	Attorney Docket No.	092459-0422/8032.US05

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.	U.S. Patent or Application NUMBER	Kind Code (if known)	Name of Patentee or Inventor of Cited Document	Date of Publication or Filing Date of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1.	5,616,330	A	Kaufman et al.	04-01-1997	
	2.	9,561,229	B2	Ottoboni et al.	02-07-2017	
	3.	9,808,465	B2	Ottoboni et al.	11-07-2017	
	4.	9,974,742	B2	Ottoboni et al.	05-22-2018	
	5.	9,974,793	B2	Ottoboni et al.	05-22-2018	
	6.	9,974,794	B2	Ottoboni et al.	05-22-2018	
	7.	10,500,208	B2	Ottoboni et al.	12-10-2019	
	8.	10,624,850	B2	Ottoboni et al.	04-21-2020	
	9.	10,953,018	B2	Ottoboni et al.	03-23-2021	
	10.	11,173,118	B2	Ottoboni et al.	11-16-2021	
	11.	11,744,800	B2	Ottoboni et al.	09-05-2023	
	12.	11,878,074	B2	Ottoboni et al.	01-23-2024	
	13.	2007/0071777	A1	Bromer et al.	03-29-2007	
	14.	2011/0009362	A1	Joshi et al.	01-13-2011	
	15.	2011/0038925	A1	Wan	02-17-2011	
	16.	2012/0045489	A1	Tong et al.	02-23-2012	
	17.	2013/0236501	A1	Booth et al.	09-12-2013	
	18.	2013/0317016	A1	Hingorani et al.	11-28-2013	
	19.	2016/0024092	A1	Wan et al.	01-28-2016	
	20.	2016/0082013	A1	Ottoboni et al.	03-24-2016	
	21.	2016/0206622	A1	Ottoboni et al.	03-24-2016	
	22.	2017/0112847	A1	Ottoboni et al.	04-27-2017	
	23.	2017/0216205	A1	Ottoboni et al.	08-03-2017	
	24.	2018/0000828	A1	Ottoboni et al.	01-04-2018	
	25.	2018/0000829	A1	Ottoboni et al.	01-04-2018	
	26.	2019/0000762	A1	Ottoboni et al.	01-03-2019	
	27.	2019/0231688	A1	Ottoboni et al.	08-01-2019	
	28.	2020/0383914	A1	Ottoboni et al.	12-10-2020	
	29.	2021/0173877	A1	Ottoboni et al.	06-10-2021	

EXAMINER	DATE CONSIDERED

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				Group Art Unit	1622
				Examiner Name	Manahil Mirghani Ali ABDALHAMEED
Sheet	2	of	4	Attorney Docket No.	092459-0422/8032.US05

U.S. PATENT DOCUMENTS

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	30.	2021/0186981	A1	Ottoboni et al.	06-24-2021	
	31.	2023/0072781	A1	Ottoboni et al.	03-09-2023	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.	Foreign Patent or Application Office	NUMBER	Kind Code (if known)	Name of Patentee or Applicant of Cited Document	Date of Publication or Filing Date of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T
	32.	CN	102379845	A	Nanjing Yoko Biolog Medical Co., Ltd.	03-21-2012		Y
	33.	CN	103520725	A	Tibet Haisco Pharm, Group Co. Ltd.	01-22-2014		*English Machine Translation*
	34.	JP	01-113315	A	Lederle Japan Ltd.	05-02-1989		*English Abstract*
	35.	JP	2005-225818	A	Otsuka Pharmaceut. Factory Inc.	08-25-2005		*English Abstract*
	36.	WO	2005/016308	A1	Chen Andrew Xian	02-24-2005		
	37.	WO	2009/124756	A1	European Molecular Biology Lab EMBL	10-15-2009		
	38.	WO	2011/158053	A1	Nanopharm Cardiovasc. Therapeutics, Ltd.	12-22-2011		
	39.	WO	2013/101749	A1	Latitude Pharmaceuticals, Inc.	07-04-2013		
	40.	WO	2013/177501	A2	Innopharma Inc.	11-28-2013		
	41.	WO	2014/005606	A1	Pharmathen SA	01-09-2014		
	42.	WO	2014/209962	A1	Tigercat Pharma, Inc.	12-31-2014		
	43.	WO	2016/044784	A1	Heron Therapeutics	03-24-2016		
	44.	WO	2017/135923	A1	Heron Therapeutics	08-10-2017		

OTHER NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume issue number(s), publisher, city and/or country where published.	
	45.	Applicant initiated interview, Examiners Summary, 31 August 2016, for U.S. Application Number: 15/083,071, now U.S. Patent Number: 9,561,229, 4 pages (2016)	

EXAMINER	DATE CONSIDERED

*EXAMINER: Initial if reference considered, whether or not criteria is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to application(s).

INFORMATION DISCLOSURE STATEMENT BY APPLICANT Form PTO-1449 (Modified) (Use several sheets if necessary)				***COMPLETE IF KNOWN***	
				Application Number	18/408,486
				Confirmation Number	5991
				Filing Date	January 9, 2024
				First Named Inventor	Thomas B. OTTOBONI
				Group Art Unit	1622
				Examiner Name	Manahil Mirghani Ali ABDALHAMEED
Sheet	3	of	4	Attorney Docket No.	092459-0422/8032.US05

OTHER NON-PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume issue number(s), publisher, city and/or country where published.	
	46.	AZIZ, "Neurokinin-1 receptor antagonists for chemotherapy-induced nausea and vomiting", Ann. Palliat. Med., Vol. 1, No. 2, pp. 130-136 (2012)	
	47.	DANDO AND PERRY, "Aprepitant: a review of its use in the prevention of chemotherapy-induced nausea and vomiting", Drugs, Vol. 64, No. 7, pp. 777-794 (2004)	
	48.	Declaration of Thomas Ottoboni under 37 C.F.R. § 1.132, filed 1 September 2016 in regard to U.S. Application Number: 15/083,071, now US Patent Number: 9,561,229, 9 pages (2016)	
	49.	Dexamethasone Sodium Phosphate retrieved from the internet from web.archive.org/web/20141224130045/http://www.drugs.com/pro/dexamethasone-sodium-phosphate.html (2017)	
	50.	CASSILETH ET AL., "Antiemetic efficacy of dexamethasone therapy in patients receiving cancer chemotherapy", Arch. Intern. Med., Vol. 143, No. 7, pp. 1347-1349 (1983) *Abstract Only*	
	51.	CURRAN ET AL., "Aprepitant: a review of its use in the prevention of nausea and vomiting", Drugs, Vol. 69, No. 13, pp. 1853-1878 (2009)	
	52.	HARGREAVES ET AL., "Development of aprepitant, the first neurokinin-1 receptor antagonist for the prevention of chemotherapy-induced nausea and vomiting", Ann. N.Y. Acad. Sci., Vol. 1222, pp. 40-48 (2011)	
	53.	International Search Report from PCT Patent Application No.: PCT/US2015/051050 mailed December 18, 2015, Application now published as International Publication No.: WO2016/044784 on 24 March 2016	
	54.	International Search Report from PCT Patent Application No.: PCT/2016/015992 mailed 3 June 2016, Application now published as International Publication No.: WO2017/135923 on 10 August 2017	
	55.	Lipoid GmbH, Lipoid Product Finder, Retrieved from the internet http://www.lipiod.com/en/node/105, 1 page (2018)	
	56.	Lipoid GmbH, Lipoid Product Finder, print friendly version, Retrieved from the internet <URL: http://www.lipoid.com/en/print/105, 2 pages (2018)	
	57.	NAVARI ET AL., "Reduction of cisplatin-induced emesis by a selective neurokinin-1-receptor antagonist. L-754,030 Antiemetic Trials Group", N. Engl. J. Med., Vol. 340, No. 3, pp. 190-195 (1999)	
	58.	SUN ET AL., "Compatibility of intravenous fosaprepitant with intravenous 5-HT3 antagonists and corticosteroids", Cancer Chemother. Pharmacol., Vol. 72, No. 3, pp. 509-513 (2013)	
	59.	TAKAGI, "New emulsification technology searching for a harmonization of formulation and mechanical emulsification method", Fragrance J., No. 19, pp. 131-138 (2005) English Abstract	
	60.	TAKAHASHI ET AL., "Pharmacokinetics of aprepitant and dexamethasone after administration of chemotherapeutic agents and effects of plasma substance P concentration on chemotherapy-induced nausea and vomiting in Japanese cancer patients", Cancer Cheother. Pharmacol., Vol. 68, No. 3, pp. 653-659 (2011)	
	61.	The Pharmaceutics and Compounding Laboratory, "Emulsions: Preparation and Stabilization, Methods of emulsion preparation", 1 page, Online article accessed 26 May 2016 from http://pharmlabs.unc.edu/labs/emulsions/prep.htm	
	62.	WENG ET AL., "Formulation, preparation, and stability of intravenous bufadienolides-loaded lipid microspheres", Eur. J. Lipid Sci., Vol. 114, pp. 1154-1164 (2012)	

EXAMINER	DATE CONSIDERED

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				Application Number	18/408,486
				Confirmation Number	5991
				Filing Date	January 9, 2024
				First Named Inventor	Thomas B. OTTOBONI
				Group Art Unit	1622
				Examiner Name	Manahil Mirghani Ali ABDALHAMEED
Sheet	4	of	4	Attorney Docket No.	092459-0422/8032.US05

OTHER NON-PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume issue number(s), publisher, city and/or country where published.	
	63.	ZHOU ET AL., "Preparation of Aprepitant emulsion for intravenous injection", Chinese Journal of Pharmaceuticals, Vol. 43, No. 12, pp. 1003-1006 (2012) *English Translation Only*	

EXAMINER	DATE CONSIDERED

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PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
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ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/408,486	05/24/2024 05:49:12 PM Z ET	092459-0422/8032.US05

Title of Invention

METHODS OF USE OF EMULSION FORMULATIONS OF AN NK-1 RECEPTOR ANTAGONIST

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	5991	FILED BY	Judy Steinkraus
PATENT CENTER #	65666173	AUTHORIZED BY	Judy Mohr
CUSTOMER #	108547	FILING DATE	01/09/2024
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Thomas B. Ottoboni

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
DA / 500417	E20245NH51219242	Judy Steinkraus

PRE-AUTHORIZED ACCOUNT	PRE-AUTHORIZED CATEGORY
500417	37 CFR 1.16 (National application filing, search, and examination fees); 37 CFR 1.17 (Patent application and reexamination processing fees); 37 CFR 1.19 (Document supply fees); 37 CFR 1.21 (Miscellaneous fees and charges)

FEE CODE	DESCRIPTION	ITEM PRICE($)	QUANTITY	ITEM TOTAL($)
2806	SUBMISSION OF AN INFORMATION DISCLOSURE STATEMENT	104.00	1	104.00
			TOTAL AMOUNT:	$104.00

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d)

and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Doc code : DISQ.EFILE
Description : Electronic Terminal Disclaimer - Approved

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Commissioner for Patents
United States Patent and Trademark Office
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APPROVAL LETTER

APPLICATION #	FILING DATE	APPLICANT/PATENT UNDER REEXAMINATION
18/408,486	01/09/2024	Thomas Ottoboni

Title of Invention

METHODS OF USE OF EMULSION FORMULATIONS OF AN NK-1 RECEPTOR ANTAGONIST

Electronic terminal disclaimer filed on 05/24/2024

☑ Approved

This patent is subject to a Terminal Disclaimer

Approved / Disapproved by: Electronic Terminal Disclaimer automatically approved

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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/408,486	**05/24/2024 06:07:45 PM Z ET**	**092459-0422/8032.US05**

Title of Invention

METHODS OF USE OF EMULSION FORMULATIONS OF AN NK-1 RECEPTOR ANTAGONIST

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	5991	FILED BY	Judy Steinkraus
PATENT CENTER #	65667093	FILING DATE	01/09/2024
CUSTOMER #	108547	FIRST NAMED INVENTOR	Thomas B. Ottoboni
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Judy Mohr

Documents

TOTAL DOCUMENTS: 2

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
petition-request.pdf	3	Terminal Disclaimer-Filed (Electronic)	55 KB
grantLetter.pdf	1	Terminal Disclaimer-Electronic-Approved	19 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
petition-request.pdf	F85F03FAB0661A8DB3103DC0D97B3BF2A6DC4249B092D9AE A2822B89A87CF2379BDCDF98C00E18B38FDDAADD73480A61

	10F0F2B4F122B0210CE8C200D9BC16A3
grantLetter.pdf	897939997A6645408F69060EABE8FF3B3DE96218A88161E368 C142D14FB07ED7F0EBBA54699639C455E8998F2F54621A2F4 A60614478F8D859B4E2E4691A8EA6

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

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ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
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Title of Invention

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PATENT CENTER #	65667093	AUTHORIZED BY	Judy Mohr
CUSTOMER #	108547	FILING DATE	01/09/2024
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Thomas B. Ottoboni

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
DA / 500417	E20245NI08199905	Judy Mohr

FEE CODE	DESCRIPTION	ITEM PRICE($)	QUANTITY	ITEM TOTAL($)
2814	STATUTORY DISCLAIMER, INCLUDING TERMINAL DISCLAIMER	170.00	1	170.00
			TOTAL AMOUNT:	$170.00

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

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TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A PRIOR PATENT

APPLICATION #	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET #
18408486	01/09/2024	Thomas Ottoboni	092459-0422/8032.US05

Title of Invention

METHODS OF USE OF EMULSION FORMULATIONS OF AN NK-1 RECEPTOR ANTAGONIST

☑ Filing of terminal disclaimer does not obviate requirement for response under 37 CFR 1.111 to outstanding Office Action

☑ This electronic Terminal Disclaimer is not being used for a Joint Research Agreement.

Owner	Percent interest
Heron Therapeutics, Inc.	100%
Total	100%

The owner(s) of percent interest listed above in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of any patent granted on pending reference Application Number(s)

Application #	Filing Date
18408463	01/09/2024
18418030	01/19/2024
18535853	12/11/2023

as the term of any patent granted on said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending reference application. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and any patent granted on the reference application are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.
In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term of any patent granted on said reference application, "as the term of any patent granted on said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending reference application," in the event that any such patent granted on the pending reference application: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321, has all claims canceled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as shortened by any terminal disclaimer filed prior to its grant.

The owner(s) of percent interest listed above in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of prior patent number(s)

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as the term of said prior patent is presently shortened by any terminal disclaimer. The owner hereby agrees that

any patent so granted on the instant application shall be enforceable only for and during such period that it and the prior patent are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.
In making the above disclaimer, the owner does not disclaim the terminal part of the term of any patent granted on the instant application that would extend to the expiration date of the full statutory term of the prior patent, "as the term of said prior patent is presently shortened by any terminal disclaimer," in the event that said prior patent later:
- expires for failure to pay a maintenance fee;
- is held unenforceable;
- is found invalid by a court of competent jurisdiction;
- is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321;
- has all claims canceled by a reexamination certificate;
- is reissued; or
- is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

☑ Terminal disclaimer fee under 37 CFR 1.20(d) included with Electronic Terminal Disclaimer request.

Applicant claims the following entity status:
Small

I hereby declare that all statements made herein of my own knowledge are true and that all statemnts made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

I certify, in accordance with 37 CFR 1.4(d)(4) that I am: An attorney or agent registered to practice before the Patent and Trademark Office who is of record in this application

Signature	Name	Registration #
/Judy Mohr/	Judy Mohr	38563

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* Statement under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner). Form PTO/SB/96 may be used for making this certification. See MPEP 324.

Notice of Allowability	Application No. 18/408,486	Applicant(s) Ottoboni et al.	
	Examiner MANAHIL M ABDALHAMEED	Art Unit 1622	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to 05/24/2024.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are 1-30 . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some* c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☑ Notice of References Cited (PTO-892)
2. ☑ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☐ Examiner's Amendment/Comment
6. ☑ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/M.M.A./ Examiner, Art Unit 1622	/BAHAR CRAIGO/ Primary Examiner, Art Unit 1699

DETAILED ACTION

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Priority

This application filed on 01/09/2024 is a continuation of U.S. Application No. 18/535,853, filed 12/11/2023, which is a continuation of U.S. Application No. 17/180,593, filed 02/19/2021 (now U.S. Patent No. 11878074), which is a continuation of U.S. Application No. 16/820,311, filed 03/16/2020 (now U.S. Patent No. 11,173,118), which is a continuation of U.S. Application No. 15/965,638, filed 04/27/2018 (now U.S. Patent No. 10,624,850), which is a continuation of U.S. Application No. 15/012,532, filed 02/01/2016 (now U.S. Patent No. 9,974,742).

DETAILED ACTION

The Amendments and Applicant's Arguments submitted on 05/24/2024 have been received and its contents have been carefully considered. Claim 7 was amended. Claims 1-30 are pending.

EXAMINER COMMENT AND REASONS FOR ALLOWANCE

Withdrawal Claim Objections

Objection of claim 7 is withdrawn in view of Applicant's amendment submitted on 05/24/2024.

Withdrawal Claim Objections – Double Patenting

Rejection of claims 1-30 rejected under the nonstatutory double patenting as being unpatentable over claims 1-21 of U.S. Patent No. 9561229B2, claims 1-6, 8-9, 12-15 of U.S. Patent No. US9808465B2,

claims 1-6, 9, and 12-14 of U.S. Patent No. 9974742B2, claims 1-22 of U.S. Patent No. 9974793B2, claims 1-11 of U.S. Patent No. 9974794B2, claims 1-5, 7-9, 11-13 of U.S. Patent No. 10500208B2, claims 1-6, 9, and 12-16 of U.S. Patent No. 10624850B2, claims 1-18 of U.S. Patent No. 10953018B2, claims 1-8, 11-12, and 14-17 of U.S. Patent No. 11173118B2, claims 1-21 of U.S. Patent No. 11744800B2, claims 1-21 of U.S. Patent No. 11878074B2, claims 1-28 of co-pending Application No. 18/408,463, claims 1-30 of co-pending Application No. 18/418,030, claims 1-20 of co-pending Application No. 18/535,853, is withdrawn in view of the Terminal Disclaimer submitted by the Applicant on 05/24/2024.

Rejection of claims 1-30 rejected under the nonstatutory double patenting as being unpatentable over claims 1-19, 21-28 of copending Application No. 17/194,114, is withdrawn because Application No. 17/194,114 is abandoned on 03/7/2024.

Rejection of claims 1-30 rejected under the nonstatutory double patenting as being unpatentable over claims 31, 39-46, 51, 54-62 and 65-71 of co-pending Application No. 16/261,459, is withdrawn because the co-pending Application No. 16/261,459 has patent term filing date of 01/29/2019, whereas the instant application has a patent term filing date of 02/01/2016, and Pursuant to MPEP 1490, the nonstatutory double patenting rejections over copending applications No. 16/261,459 is withdrawn because the instant application has an earlier patent term filing date.

Terminal Disclaimer

The terminal disclaimer filed on 05/24/2024 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of any patent granted on U.S. Patent No. US9561229B2, US9808465B2, US9974742B2, US9974793B2, US9974794B2, US10500208B2, US10624850B2, US10953018B2, US11173118B2, US11744800B2, US11878074B2, and U. S. Application Number 18/408,463, 18/418,030, and 18/535,853 has been reviewed and is accepted. The terminal disclaimer has been recorded.

Reasons for Allowance

The following is an examiner's statement of reasons for allowance:

The closest prior art is considered to be W. Zhou et al. (CN102379845A, 03/21/2012).

Zhou teaches NK-1 antagonist, aprepitant microemulsion for injection, consisting of 0.05% ~ 2% aprepitant, 5% ~ 30% injection oil, 0.5% ~ 10% emulsification Agent, 1-10% emulsion aid, 5% -20% protective agent; 60-80% water for injection. Zhou teaches that the emulsifier is egg yolk phospholipid, the oil is soybean oil, and teaches that the emulsion comprises alcohol (ethanol) and a pH modifier, wherein the NK-1 antagonist aprepitant is used to treat patients at risk of vomiting induced by cancer chemotherapy.

However, Zhou's ratio of emulsifier to aprepitant (the NK-1 antagonist) is below the ratio required by the claimed invention. It appears that the amount of emulsifier is critical in the claimed emulsion because, according to the instant specification, the aprepitant emulsion possess favorable stability properties when the amount of emulsifier in the oil phase is greater than the amount of oil, wherein the amount of emulsifier have been found to impart greater stability on a final emulsion compared to a similar aprepitant emulsion with the oil phase comprises emulsifier less than the claimed amount. [Instant specification, pg. 16, 0099]. For example, the instant specification provides preparation of an alternate aprepitant emulsion, wherein the ratio of aprepitant: emulsion is 1: 14.8, wherein with 4 days post preparation, crystals were observed which indicates less stable emulsion. [Instant Specification, Example 4, pg. 28].

In order to arrive at the claimed composition, one of ordinary skill in the art would have to modify

Zhou's aprepitant emulsion to increase the ratio of the emulsifier to the NK-1 receptor antagonist to about 18:1 to 22:1 (wt/wt%). However, neither Zhou's disclosure, nor this disclosure provides sufficient guidance and motivation to one of ordinary skill in the art to perform the modification to arrive at instantly claimed emulsion.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MANAHIL MIRGHANI ALI ABDALHAMEED whose telephone number is (571)272-1242. The examiner can normally be reached M-F 7:30 am - 5:00 pm.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Havlin can be reached on 571-272-9066. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: https://patentcenter.uspto.gov. Visit https://www.uspto.gov/patents/apply/patent-center for more information about Patent Center and https://www.uspto.gov/patents/docx for information about filing in DOCX format. For additional

questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/M.M.A./
Examiner, Art Unit 1622

/BAHAR CRAIGO/
Primary Examiner, Art Unit 1699

Notice of References Cited	Application/Control No. 18/408,486	Applicant(s)/Patent Under Reexamination Ottoboni et al.	
	Examiner MANAHIL M ABDALHAMEED	Art Unit 1622	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date YYYY-MM-DD	Name	CPC Classification	US Classification
	A					
	B					
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FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date YYYY-MM-DD	Country	Name	CPC Classification
	N	CN-102379845-A	2012-03-21	CN	CAO Y	
	O					
	P					
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NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in YYYY-MM-DD format are publication dates. Classifications may be US or foreign.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT Form PTO-1449 (Modified) (Use several sheets if necessary)				COMPLETE IF KNOWN	
				Application Number	18/408,486
				Confirmation Number	5991
				Filing Date	January 9, 2024
				First Named Inventor	Thomas B. OTTOBONI
				Group Art Unit	1622
				Examiner Name	Manahil Mirghani Ali ABDALHAMEED
Sheet	1	of	4	Attorney Docket No.	092459-0422/8032.US05

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.	U.S. Patent or Application NUMBER	Kind Code (if known)	Name of Patentee or Inventor of Cited Document	Date of Publication or Filing Date of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1.	5,616,330	A	Kaufman et al.	04-01-1997	
	2.	9,561,229	B2	Ottoboni et al.	02-07-2017	
	3.	9,808,465	B2	Ottoboni et al.	11-07-2017	
	4.	9,974,742	B2	Ottoboni et al.	05-22-2018	
	5.	9,974,793	B2	Ottoboni et al.	05-22-2018	
	6.	9,974,794	B2	Ottoboni et al.	05-22-2018	
	7.	10,500,208	B2	Ottoboni et al.	12-10-2019	
	8.	10,624,850	B2	Ottoboni et al.	04-21-2020	
	9.	10,953,018	B2	Ottoboni et al.	03-23-2021	
	10.	11,173,118	B2	Ottoboni et al.	11-16-2021	
	11.	11,744,800	B2	Ottoboni et al.	09-05-2023	
	12.	11,878,074	B2	Ottoboni et al.	01-23-2024	
	13.	2007/0071777	A1	Bromer et al.	03-29-2007	
	14.	2011/0009362	A1	Joshi et al.	01-13-2011	
	15.	2011/0038925	A1	Wan	02-17-2011	
	16.	2012/0045489	A1	Tong et al.	02-23-2012	
	17.	2013/0236501	A1	Booth et al.	09-12-2013	
	18.	2013/0317016	A1	Hingorani et al.	11-28-2013	
	19.	2016/0024092	A1	Wan et al.	01-28-2016	
	20.	2016/0082013	A1	Ottoboni et al.	03-24-2016	
	21.	2016/0206622	A1	Ottoboni et al.	03-24-2016	
	22.	2017/0112847	A1	Ottoboni et al.	04-27-2017	
	23.	2017/0216205	A1	Ottoboni et al.	08-03-2017	
	24.	2018/0000828	A1	Ottoboni et al.	01-04-2018	
	25.	2018/0000829	A1	Ottoboni et al.	01-04-2018	
	26.	2019/0000762	A1	Ottoboni et al.	01-03-2019	
	27.	2019/0231688	A1	Ottoboni et al.	08-01-2019	
	28.	2020/0383914	A1	Ottoboni et al.	12-10-2020	
	29.	2021/0173877	A1	Ottoboni et al.	06-10-2021	

EXAMINER	DATE CONSIDERED
/MANAHIL MIRGHANI ALI ABDALHAMEED/	06/04/2024

*EXAMINER: Initial if reference considered, whether or not criteria is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to application(s).

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.M.A./

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Sheet	2	of	4	Attorney Docket No.	092459-0422/8032.US05

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	30.	2021/0186981	A1	Ottoboni et al.	06-24-2021	
	31.	2023/0072781	A1	Ottoboni et al.	03-09-2023	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.	Foreign Patent or Application Office	NUMBER	Kind Code (if known)	Name of Patentee or Applicant of Cited Document	Date of Publication or Filing Date of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T
	32.	CN	102379845	A	Nanjing Yoko Biolog Medical Co., Ltd.	03-21-2012		Y
	33.	CN	103520725	A	Tibet Haisco Pharm, Group Co. Ltd.	01-22-2014		*English Machine Translation*
	34.	JP	01-113315	A	Lederle Japan Ltd.	05-02-1989		*English Abstract*
	35.	JP	2005-225818	A	Otsuka Pharmaceut. Factory Inc.	08-25-2005		*English Abstract*
	36.	WO	2005/016308	A1	Chen Andrew Xian	02-24-2005		
	37.	WO	2009/124756	A1	European Molecular Biology Lab EMBL	10-15-2009		
	38.	WO	2011/158053	A1	Nanopharm Cardiovasc. Therapeutics, Ltd.	12-22-2011		
	39.	WO	2013/101749	A1	Latitude Pharmaceuticals, Inc.	07-04-2013		
	40.	WO	2013/177501	A2	Innopharma Inc.	11-28-2013		
	41.	WO	2014/005606	A1	Pharmathen SA	01-09-2014		
	42.	WO	2014/209962	A1	Tigercat Pharma, Inc.	12-31-2014		
	43.	WO	2016/044784	A1	Heron Therapeutics	03-24-2016		
	44.	WO	2017/135923	A1	Heron Therapeutics	08-10-2017		

OTHER NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume issue number(s), publisher, city and/or country where published.	
	45.	Applicant initiated interview, Examiners Summary, 31 August 2016, for U.S. Application Number: 15/083,071, now U.S. Patent Number: 9,561,229, 4 pages (2016)	

EXAMINER	DATE CONSIDERED
/MANAHIL MIRGHANI ALI ABDALHAMEED/	06/04/2024

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Sheet	3	of	4	Attorney Docket No.	092459-0422/8032.US05

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	46.	AZIZ, "Neurokinin-1 receptor antagonists for chemotherapy-induced nausea and vomiting", Ann. Palliat. Med., Vol. 1, No. 2, pp. 130-136 (2012)	
	47.	DANDO AND PERRY, "Aprepitant: a review of its use in the prevention of chemotherapy-induced nausea and vomiting", Drugs, Vol. 64, No. 7, pp. 777-794 (2004)	
	48.	Declaration of Thomas Ottoboni under 37 C.F.R. § 1.132, filed 1 September 2016 in regard to U.S. Application Number: 15/083,071, now US Patent Number: 9,561,229, 9 pages (2016)	
	49.	Dexamethasone Sodium Phosphate retrieved from the internet from web.archive.org/web/20141224130045/http://www.drugs.com/pro/dexamethasone-sodium-phosphate.html (2017)	
	50.	CASSILETH ET AL., "Antiemetic efficacy of dexamethasone therapy in patients receiving cancer chemotherapy", Arch. Intern. Med., Vol. 143, No. 7, pp. 1347-1349 (1983) *Abstract Only*	
	51.	CURRAN ET AL., "Aprepitant: a review of its use in the prevention of nausea and vomiting", Drugs, Vol. 69, No. 13, pp. 1853-1878 (2009)	
	52.	HARGREAVES ET AL., "Development of aprepitant, the first neurokinin-1 receptor antagonist for the prevention of chemotherapy-induced nausea and vomiting", Ann. N.Y. Acad. Sci., Vol. 1222, pp. 40-48 (2011)	
	53.	International Search Report from PCT Patent Application No.: PCT/US2015/051050 mailed December 18, 2015, Application now published as International Publication No.: WO2016/044784 on 24 March 2016	
	54.	International Search Report from PCT Patent Application No.: PCT/2016/015992 mailed 3 June 2016, Application now published as International Publication No.: WO2017/135923 on 10 August 2017	
	55.	Lipoid GmbH, Lipoid Product Finder, Retrieved from the internet http://www.lipiod.com/en/node/105, 1 page (2018)	
	56.	Lipoid GmbH, Lipoid Product Finder, print friendly version, Retrieved from the internet <URL: http://www.lipoid.com/en/print/105, 2 pages (2018)	
	57.	NAVARI ET AL., "Reduction of cisplatin-induced emesis by a selective neurokinin-1-receptor antagonist. L-754,030 Antiemetic Trials Group", N. Engl. J. Med., Vol. 340, No. 3, pp. 190-195 (1999)	
	58.	SUN ET AL., "Compatibility of intravenous fosaprepitant with intravenous 5-HT3 antagonists and corticosteroids", Cancer Chemother. Pharmacol., Vol. 72, No. 3, pp. 509-513 (2013)	
	59.	TAKAGI, "New emulsification technology searching for a harmonization of formulation and mechanical emulsification method", Fragrance J., No. 19, pp. 131-138 (2005) English Abstract	
	60.	TAKAHASHI ET AL., "Pharmacokinetics of aprepitant and dexamethasone after administration of chemotherapeutic agents and effects of plasma substance P concentration on chemotherapy-induced nausea and vomiting in Japanese cancer patients", Cancer Cheother. Pharmacol., Vol. 68, No. 3, pp. 653-659 (2011)	
	61.	The Pharmaceutics and Compounding Laboratory, "Emulsions: Preparation and Stabilization, Methods of emulsion preparation", 1 page, Online article accessed 26 May 2016 from http://pharmlabs.unc.edu/labs/emulsions/prep.htm	
	62.	WENG ET AL., "Formulation, preparation, and stability of intravenous bufadienolides-loaded lipid microspheres", Eur. J. Lipid Sci., Vol. 114, pp. 1154-1164 (2012)	

EXAMINER	DATE CONSIDERED
/MANAHIL MIRGHANI ALI ABDALHAMEED/	06/04/2024

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				Group Art Unit	1622
				Examiner Name	Manahil Mirghani Ali ABDALHAMEED
Sheet	4	of	4	Attorney Docket No.	092459-0422/8032.US05

OTHER NON-PATENT LITERATURE DOCUMENTS			
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	63.	ZHOU ET AL., "Preparation of Aprepitant emulsion for intravenous injection", Chinese Journal of Pharmaceuticals, Vol. 43, No. 12, pp. 1003-1006 (2012) *English Translation Only*	

EXAMINER	DATE CONSIDERED
/MANAHIL MIRGHANI ALI ABDALHAMEED/	06/04/2024

*EXAMINER: Initial if reference considered, whether or not criteria is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to application(s).

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.M.A./

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

108547 7590 06/20/2024

McDermott Will & Emery LLP
500 North Capitol Street NW
Washington, DC 20001-1531

EXAMINER	
ABDALHAMEED, MANAHIL MIRGHANI ALI	
ART UNIT	**PAPER NUMBER**
1622	

DATE MAILED: 06/20/2024

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/408,486	01/09/2024	Thomas B. Ottoboni	092459-0422/8032.US05	5991

TITLE OF INVENTION: METHODS OF USE OF EMULSION FORMULATIONS OF AN NK-1 RECEPTOR ANTAGONIST

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$480	$0.00	$0.00	$480	09/20/2024

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 40% the amount of undiscounted fees, and micro entity fees are 20% the amount of undiscounted fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via the USPTO patent electronic filing system.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications. **Because electronic patent issuance may occur shortly after issue fee payment, any desired continuing application should preferably be filed prior to payment of this issue fee in order not to jeopardize copendency.**

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

108547 7590 06/20/2024
McDermott Will & Emery LLP
500 North Capitol Street NW
Washington, DC 20001-1531

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via the USPTO patent electronic filing system or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/408,486	01/09/2024	Thomas B. Ottoboni	092459-0422/8032.US05	5991

TITLE OF INVENTION: METHODS OF USE OF EMULSION FORMULATIONS OF AN NK-1 RECEPTOR ANTAGONIST

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$480	$0.00	$0.00	$480	09/20/2024

EXAMINER	ART UNIT	CLASS-SUBCLASS
ABDALHAMEED, MUKHLAN AL	1622	707-750000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/AIA/122 or PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. Fees submitted: ❑Issue Fee ❑Publication Fee (if required)

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

❑ Electronic Payment via the USPTO patent electronic filing system ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29
NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

❑ Applicant asserting small entity status. See 37 CFR 1.27
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

❑ Applicant changing to regular undiscounted fee status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/408,486	01/09/2024	Thomas B. Ottoboni	092459-0422/8032.US05	5991

108547 7590 06/20/2024

McDermott Will & Emery LLP
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Washington, DC 20001-1531

EXAMINER	
ABDALHAMEED, MANAHIL MIRGHANI ALI	
ART UNIT	PAPER NUMBER
1622	

DATE MAILED: 06/20/2024

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. The United States Patent and Trademark Office (USPTO) collects the information in this record under authority of 35 U.S.C. 2. The USPTO's system of records is used to manage all applicant and owner information including name, citizenship, residence, post office address, and other information with respect to inventors and their legal representatives pertaining to the applicant's/owner's activities in connection with the invention for which a patent is sought or has been granted. The applicable Privacy Act System of Records Notice for the information collected in this form is COMMERCE/PAT-TM-7 Patent Application Files, available in the Federal Register at 78 FR 19243 (March 29, 2013).
https://www.govinfo.gov/content/pkg/FR-2013-03-29/pdf/2013-07341.pdf

Routine uses of the information in this record may include disclosure to:

1) law enforcement, in the event that the system of records indicates a violation or potential violation of law;
2) a federal, state, local, or international agency, in response to its request;
3) a contractor of the USPTO having need for the information in order to perform a contract;
4) the Department of Justice for determination of whether the Freedom of Information Act (FOIA) requires disclosure of the record;
5) a Member of Congress submitting a request involving an individual to whom the record pertains, when the individual has requested the Member's assistance with respect to the subject matter of the record;
6) a court, magistrate, or administrative tribunal, in the course of presenting evidence, including disclosures to opposing counsel in the course of settlement negotiations;
7) the Administrator, General Services Administration (GSA), or their designee, during an inspection of records conducted by GSA under authority of 44 U.S.C. 2904 and 2906, in accordance with the GSA regulations and any other relevant (i.e., GSA or Commerce) directive, where such disclosure shall not be used to make determinations about individuals;
8) another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c));
9) the Office of Personnel Management (OPM) for personnel research purposes; and
10) the Office of Management and Budget (OMB) for legislative coordination and clearance.

If you do not furnish the information requested on this form, the USPTO may not be able to process and/or examine your submission, which may result in termination of proceedings, abandonment of the application, and/or expiration of the patent.

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/408,486	**09/10/2024 08:24:00 PM Z ET**	**092459-0422/8032.US05**

Title of Invention

METHODS OF USE OF EMULSION FORMULATIONS OF AN NK-1 RECEPTOR ANTAGONIST

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	5991	FILED BY	Vickie Wall
PATENT CENTER #	67113432	AUTHORIZED BY	Judy Mohr
CUSTOMER #	108547	FILING DATE	01/09/2024
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Thomas B. Ottoboni

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
DA / 500417	**E202490K25195756**	**Vickie Wall**

FEE CODE	DESCRIPTION	ITEM PRICE($)	QUANTITY	ITEM TOTAL($)
2501	UTILITY ISSUE FEE	480.00	1	480.00
			TOTAL AMOUNT:	**$480.00**

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/408,486	**09/10/2024 08:24:00 PM Z ET**	**092459-0422/8032.US05**

Title of Invention

METHODS OF USE OF EMULSION FORMULATIONS OF AN NK-1 RECEPTOR ANTAGONIST

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CONFIRMATION #	5991	FILED BY	Vickie Wall
PATENT CENTER #	67113432	FILING DATE	01/09/2024
CUSTOMER #	108547	FIRST NAMED INVENTOR	Thomas B. Ottoboni
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Judy Mohr

Documents

TOTAL DOCUMENTS: 1

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
092459-0422_8032.US05_IssueFeeTrans.pdf	1	Issue Fee Payment (PTO-85B)	143 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
092459-0422_8032.US05_IssueFeeTrans.pdf	5711FCF3BD1602FFE68EE80A35BAB63351E96369D05A58F63C1F88275CD9DEE7D394D386E1AD9B27775CDF5B515E84F5B3789E471A0B2CCDA7A1206EE2E486C7

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PART B - FEE(S) TRANSMITTAL

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By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
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Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications. **Because electronic patent issuance may occur shortly after issue fee payment, any desired continuing application should preferably be filed prior to payment of this issue fee in order not to jeopardize copendency.**

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

108547 7590 06/20/2024
McDermott Will & Emery LLP
500 North Capitol Street NW
Washington, DC 20001-1531

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via the USPTO patent electronic filing system or by facsimile to (571) 273-2885, on the date below.

Vickie D. Wall	(Typed or printed name)
/Vickie D. Wall/	(Signature)
September 10, 2024	(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/408,486	01/09/2024	Thomas B. Ottoboni	092459-0422/8032.US05	5991

TITLE OF INVENTION: METHODS OF USE OF EMULSION FORMULATIONS OF AN NK-1 RECEPTOR ANTAGONIST

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nonprovisional	SMALL	$480	$0.00	$0.00	$480	09/20/2024

EXAMINER	ART UNIT	CLASS-SUBCLASS
ABDALHAMEED,	1622	707-750000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/AIA/122 or PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 McDermott Will & Emery
2
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: Heron Therapeutics, Inc.
(B) RESIDENCE: (CITY and STATE OR COUNTRY): San Diego, CA

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. Fees submitted: ☒ Issue Fee ☐ Publication Fee (if required)

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

☒ Electronic Payment via the USPTO patent electronic filing system ☐ Enclosed check ☐ Non-electronic payment by credit card (Attach form PTO-2038)

☒ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. 50-0417

5. **Change in Entity Status** (from status indicated above)

☐ Applicant certifying micro entity status. See 37 CFR 1.29
NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

☐ Applicant asserting small entity status. See 37 CFR 1.27
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

☐ Applicant changing to regular undiscounted fee status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature /Judy M. Mohr/ Date September 10, 2024

Typed or printed name Judy M. Mohr Registration No. 38563

PTOL-85 Part B (11/23) Approved for use through 03/31/2026 OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/408,486	10/15/2024	12115254	092459-0422/8032.US05	5991

108547 7590 09/25/2024

McDermott Will & Emery LLP
500 North Capitol Street NW
Washington, DC 20001-1531

ISSUE NOTIFICATION

The projected patent number and issue date are specified above. The patent will issue electronically. The electronically issued patent is the official patent grant pursuant to 35 U.S.C. § 153. The patent may be accessed on or after the issue date through Patent Center at https://patentcenter.uspto.gov/. The patent will be available in both the public and the private sides of Patent Center. Further assistance in electronically accessing the patent, or about Patent Center, is available by calling the Patent Electronic Business Center at 1-888-217-9197.

The USPTO is implementing electronic patent issuance with a transition period, during which period the USPTO will mail a ceremonial paper copy of the electronic patent grant to the correspondence address of record. Additional copies of the patent (i.e., certified and presentation copies) may be ordered for a fee from the USPTO's Certified Copy Center at https://certifiedcopycenter.uspto.gov/index.html. The Certified Copy Center may be reached at (800)972-6382.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Center (https://patentcenter.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Patents Stakeholder Experience (OPSE), Stakeholder Support Division (SSD) at (571)-272-4200.

IR103 (Rev. 10/09)

INVENTOR(s) (Please see PATENT CENTER site https://patentcenter.uspto.gov for additional inventors):

Thomas B. Ottoboni, Belmont, CA;
Han Han, Sunnyvale, CA;

APPLICANT(s) (Please see PATENT CENTER site https://patentcenter.uspto.gov for additional applicants):

Heron Therapeutics, Inc., San Diego, CA;

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The USA offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to encourage and facilitate business investment. To learn more about why the USA is the best country in the world to develop technology, manufacture products, and grow your business, visit SelectUSA.gov.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/408,486	01/09/2024	Thomas B. Ottoboni	092459-0422/8032.US05	5991

108547 7590 10/15/2024

McDermott Will & Emery LLP
500 North Capitol Street NW
Washington, DC 20001-1531

EXAMINER
ABDALHAMEED, MANAHIL MIRGHANI ALI

ART UNIT	PAPER NUMBER
1622	

NOTIFICATION DATE	DELIVERY MODE
10/15/2024	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ipdocketmwe@mwe.com

PTOL-90A (Rev. 04/07)

APPLICATION NO.	ISSUE DATE	PATENT NO.
18/408,486	15-Oct-2024	12115254

McDermott Will & Emery LLP
500 North Capitol Street NW
Washington, DC 20001-1531

EGRANT NOTIFICATION

Your electronic patent grant (eGrant) is now available, which can be accessed via Patent Center at https://patentcenter.uspto.gov

The electronic patent grant is the official patent grant under 35 U.S.C. 153. For more information, please visit https://www.uspto.gov/electronicgrants

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 18/408,486

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	64		N/A	
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	280		N/A	
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	320		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	30 minus 20 =	* 10	x 40 =	400	OR		
INDEPENDENT CLAIMS (37 CFR 1.16(h))	3 minus 3 =	*	x =	0			
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			0			
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				0			
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	1064		TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	18/408,486	Ottoboni et al.
	Examiner	Art Unit
	MANAHIL M ABDALHAMEED	1622

CPC - Searched*		
Symbol	Date	Examiner
A61K9/1075	03/12/2024	MMA
A61K9/0019	03/12/2024	MMA
A61K31/43	03/12/2024	MMA
A61K31/496	03/12/2024	MMA
A61K31/5377	03/12/2024	MMA
A61K47/10	03/12/2024	MMA
A61K47/44	03/12/2024	MMA

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
SEARCH, Classification and Limited Classification search, Assignee search, Inventor search (DAV), see attached	03/12/2024	MMA
STNext search, see attached	03/12/2024	MMA

/M.M.A./ Examiner, Art Unit 1622	

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	18/408,486	Ottoboni et al.
	Examiner	Art Unit
	MANAHIL M ABDALHAMEED	1622

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
A61K	9	03/12/2024	MMA

/M.M.A./ Examiner, Art Unit 1622	

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
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A61K31/496	03/12/2024	MMA
A61K31/5377	03/12/2024	MMA
A61K47/10	03/12/2024	MMA
A61K47/44	03/12/2024	MMA

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
SEARCH, Classification and Limited Classification search, Assignee search, Inventor search (DAV), see attached	03/12/2024	MMA
STNext search, see attached	03/12/2024	MMA
PE2E SEARCH, Assignee search, Inventor search (DAV), see attached	06/03/2024	MMA
STNext search, see attached	06/03/2024	MMA

/M.M.A./ Examiner, Art Unit 1622	/BAHAR CRAIGO/ Primary Examiner, Art Unit 1699

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	18/408,486	Ottoboni et al.
	Examiner	Art Unit
	MANAHIL M ABDALHAMEED	1622

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
A61K	9	03/12/2024	MMA

/M.M.A./ Examiner, Art Unit 1622	/BAHAR CRAIGO/ Primary Examiner, Art Unit 1699

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	18/408,486	Ottoboni et al.
	Examiner	**Art Unit**
	MANAHIL M ABDALHAMEED	1622

CPC							
Symbol						**Type**	**Version**
A61K	/	9	/	1075		F	2013-01-01
A61K	/	9	/	0019		I	2013-01-01
A61K	/	47	/	24		I	2013-01-01
A61K	/	47	/	44		I	2013-01-01
A61K	/	47	/	10		I	2013-01-01
A61K	/	31	/	435		I	2013-01-01
A61K	/	31	/	496		I	2013-01-01
A61K	/	31	/	43		I	2013-01-01
A61K	/	31	/	5377		I	2013-01-01
A61K	/	31	/	573		I	2013-01-01
G06F	/	16	/	9038		I	2019-01-01
G06N	/	20	/	00		I	2019-01-01
G06F	/	16	/	90344		I	2019-01-01

CPC Combination Sets								
Symbol					**Type**	**Set**	**Ranking**	**Version**
A61K	/	31	/	5377	I	1	1	2013-01-01
A61K	/	2300	/	00	I	1	2	2013-01-01
A61K	/	31	/	573	I	2	1	2013-01-01
A61K	/	2300	/	00	I	2	2	2013-01-01
A61K	/	31	/	435	I	3	1	2013-01-01
A61K	/	2300	/	00	I	3	2	2013-01-01
A61K	/	31	/	496	I	4	1	2013-01-01
A61K	/	2300	/	00	I	4	2	2013-01-01

/MANAHIL MIRGHANI ALI ABDALHAMEED/ Examiner, Art Unit 1622	04 June 2024	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	30	
/BAHAR CRAIGO/ Primary Examiner, Art Unit 1699	10 June 2024	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	None

U.S. Patent and Trademark Office — Part of Paper No.: 20240604

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	18/408,486	Ottoboni et al.
	Examiner	**Art Unit**
	MANAHIL M ABDALHAMEED	1622

INTERNATIONAL CLASSIFICATION					
CLAIMED					
A61K9/107	/	9	/	107	

NON-CLAIMED					
	/		/		

US ORIGINAL CLASSIFICATION	
CLASS	**SUBCLASS**

CROSS REFERENCES(S)						
CLASS	**SUBCLASS (ONE SUBCLASS PER BLOCK)**					

/MANAHIL MIRGHANI ALI ABDALHAMEED/ Examiner, Art Unit 1622	04 June 2024	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	30	
/BAHAR CRAIGO/ Primary Examiner, Art Unit 1699	10 June 2024	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	None

U.S. Patent and Trademark Office — Part of Paper No.: 20240604

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	18/408,486	Ottoboni et al.
	Examiner	**Art Unit**
	MANAHIL M ABDALHAMEED	1622

☑ Claims renumbered in the same order as presented by applicant ☐ CPA ☑ T.D. ☐ R.1.47

CLAIMS

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	1	10	10	19	19	28	28								
2	2	11	11	20	20	29	29								
3	3	12	12	21	21	30	30								
4	4	13	13	22	22										
5	5	14	14	23	23										
6	6	15	15	24	24										
7	7	16	16	25	25										
8	8	17	17	26	26										
9	9	18	18	27	27										

/MANAHIL MIRGHANI ALI ABDALHAMEED/ Examiner, Art Unit 1622	04 June 2024	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	30	
/BAHAR CRAIGO/ Primary Examiner, Art Unit 1699	10 June 2024	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	None

U.S. Patent and Trademark Office — Part of Paper No.: 20240604

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
092459-0175		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US2016/015992	1 February 2016 (01-02-2016)	
Applicant		
HERON THERAPEUTICS, INC.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language,** the international search was carried out on the basis of:
      [X] the international application in the language in which it was filed
      [ ] a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. [ ] This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [ ] **Certain claims were found unsearchable** (See Box No. II)

3. [ ] **Unity of invention is lacking** (see Box No III)

4. With regard to the **title,**
   [ ] the text is approved as submitted by the applicant
   [X] the text has been established by this Authority to read as follows:

   EMULSION COMPRISING AN NK-1 RECEPTOR ANTAGONIST

5. With regard to the **abstract,**
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings,**
   a. the figure of the **drawings** to be published with the abstract is Figure No. _____
      [ ] as suggested by the applicant
      [ ] as selected by this Authority, because the applicant failed to suggest a figure
      [ ] as selected by this Authority, because this figure better characterizes the invention
   b. [X] none of the figures is to be published with the abstract

Form PCT/ISA/210 (first sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2016/015992

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/00 A61K47/24 A61K9/107 A61K31/454 A61K31/496 A61K31/5377
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2016/024092 A1 (WAN JIANSHENG [US] ET AL) 28 January 2016 (2016-01-28)	18-25
A	figure 3 paragraph [0004] examples 1-7	1-17, 26-28
A	CN 102 379 845 A (NANJING YOKO BIOLOG MEDICAL CO LTD) 21 March 2012 (2012-03-21) the whole document	1-28
A	US 2013/317016 A1 (HINGORANI TUSHAR [US] ET AL) 28 November 2013 (2013-11-28) paragraph [0054] - paragraph [0056]	1-28
A	WO 2014/209962 A1 (TIGERCAT PHARMA INC [US]) 31 December 2014 (2014-12-31) example 4 table 7	1-28

-/--

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 May 2016	03/06/2016

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Sindel, Ulrike

1

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2016/015992

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2014/005606 A1 (PHARMATHEN SA [GR]; KARAVAS EVANGELOS [GR]; KOUTRIS EFTHIMOS [GR]; BIK) 9 January 2014 (2014-01-09) claims 1-3	1-28
E	WO 2016/044784 A1 (HERON THERAPEUTICS INC [US]) 24 March 2016 (2016-03-24) claims 1-17	1-9, 11-16, 18-23, 26-28

1

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2016/015992

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2016024092 A1	28-01-2016	AU 2010282483 A1	01-03-2012
		BR 112012003263 A2	22-09-2015
		CA 2770403 A1	17-02-2011
		CN 102573475 A	11-07-2012
		CN 105503870 A	20-04-2016
		EP 2464230 A1	20-06-2012
		JP 5860399 B2	16-02-2016
		JP 2013501806 A	17-01-2013
		JP 2016041734 A	31-03-2016
		KR 20120060215 A	11-06-2012
		RU 2012109405 A	20-09-2013
		SG 178403 A1	29-03-2012
		SG 10201407538W A	29-01-2015
		TW 201111382 A	01-04-2011
		TW 201604195 A	01-02-2016
		US 2011038925 A1	17-02-2011
		US 2016024092 A1	28-01-2016
		WO 2011019911 A1	17-02-2011
CN 102379845 A	21-03-2012	NONE	
US 2013317016 A1	28-11-2013	AU 2013266141 A1	11-12-2014
		CA 2874700 A1	28-11-2013
		CN 104619312 A	13-05-2015
		EP 2855436 A2	08-04-2015
		HK 1203193 A1	23-10-2015
		JP 2015521190 A	27-07-2015
		KR 20150022839 A	04-03-2015
		NZ 702114 A	26-02-2016
		SG 11201407765V A	29-01-2015
		US 2013317016 A1	28-11-2013
		WO 2013177501 A2	28-11-2013
WO 2014209962 A1	31-12-2014	AU 2014302694 A1	07-01-2016
		CA 2915474 A1	31-12-2014
		CN 105473138 A	06-04-2016
		EP 3013336 A1	04-05-2016
		KR 20160023692 A	03-03-2016
		PH 12015502777 A1	21-03-2016
		WO 2014209962 A1	31-12-2014
WO 2014005606 A1	09-01-2014	EP 2866797 A1	06-05-2015
		US 2015165045 A1	18-06-2015
		WO 2014005606 A1	09-01-2014
WO 2016044784 A1	24-03-2016	US 2016082013 A1	24-03-2016
		WO 2016044784 A1	24-03-2016

Form PCT/ISA/210 (patent family annex) (April 2005)

Information on Search Strategy - Pilot phase (see OJ 2015, A86)
The type of information contained in this sheet may change during the pilot for improving the usefulness of this new service.

Application Number
PCT/US2016/015992

TITLE: EMULSION COMPRISING AN NK-1 RECEPTOR ANTAGONIST

APPLICANT: HERON THERAPEUTICS, INC.

IPC CLASSIFICATION: A61K9/00, A61K47/24, A61K9/107, A61K31/454, A61K31/496, A61K31/5377

EXAMINER: Sindel, Ulrike

CONSULTED DATABASES:

CLASSIFICATION SYMBOLS DEFINING EXTENT OF THE SEARCH:

IPC:

CPC: A61K9/0019, A61K47/24, A61K9/1075, A61K31/454, A61K31/496, A61K31/5377

FI/F-TERMS:

KEYWORDS OR OTHER ELEMENTS FEATURING THE INVENTION:

EPO FORM F04442

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
092459-0171		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US2015/051050	18 September 2015 (18-09-2015)	19 September 2014 (19-09-2014)
Applicant		
HERON THERAPEUTICS, INC.		

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      [ ] as suggested by the applicant
      [ ] as selected by this Authority, because the applicant failed to suggest a figure
      [ ] as selected by this Authority, because this figure better characterizes the invention
   b. [X] none of the figures is to be published with the abstract

Form PCT/ISA/210 (first sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2015/051050

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/00 A61K47/10 A61K47/44 A61K47/24 A61K47/12 A61K47/26
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2014/005606 A1 (PHARMATHEN SA [GR]; KARAVAS EVANGELOS [GR]; KOUTRIS EFTHIMOS [GR]; BIK) 9 January 2014 (2014-01-09) the whole document claim 1; table 9 -----	1-17
X	WO 2013/177501 A2 (INNOPHARMA INC [US]) 28 November 2013 (2013-11-28) the whole document paragraph [0032]; claims 1,2 -----	1-17
X	WO 2011/158053 A1 (NANOFORM CARDIOVASCULAR THERAPEUTICS LTD [GB]; FILIPCSEI GENOVEVA [HU]) 22 December 2011 (2011-12-22) the whole document example 5 ----- -/--	1-17

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 December 2015	18/12/2015

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Giese, Hans-Hermann

1

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CN 102 379 845 A (NANJING YOKO BIOLOG MEDICAL CO LTD) 21 March 2012 (2012-03-21) the whole document claim 1; example 1	1-17
A	WO 2005/016308 A1 (CHEN ANDREW XIAN [US]) 24 February 2005 (2005-02-24) claims; examples 6,8	1
A	WO 2009/124756 A1 (EUROPEAN MOLECULAR BIOLOGY LAB EMBL [DE]; UNIV MODENA E REGGIO EMILIA) 15 October 2009 (2009-10-15) the whole document	1

1

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2014005606 A1	09-01-2014	EP 2866797 A1	06-05-2015
		US 2015165045 A1	18-06-2015
		WO 2014005606 A1	09-01-2014
WO 2013177501 A2	28-11-2013	AU 2013266141 A1	11-12-2014
		CA 2874700 A1	28-11-2013
		CN 104619312 A	13-05-2015
		EP 2855436 A2	08-04-2015
		HK 1203193 A1	23-10-2015
		IL 235864 A	01-02-2015
		JP 2015521190 A	27-07-2015
		KR 20150022839 A	04-03-2015
		SG 11201407765V A	29-01-2015
		US 2013317016 A1	28-11-2013
		WO 2013177501 A2	28-11-2013
WO 2011158053 A1	22-12-2011	AU 2011266808 A1	07-02-2013
		CN 103097379 A	08-05-2013
		EP 2582697 A1	24-04-2013
		JP 2013528642 A	11-07-2013
		RU 2013102030 A	27-07-2014
		SG 186377 A1	30-01-2013
		US 2013209521 A1	15-08-2013
		WO 2011158053 A1	22-12-2011
CN 102379845 A	21-03-2012	NONE	
WO 2005016308 A1	24-02-2005	CA 2576060 A1	24-02-2005
		EP 1651186 A1	03-05-2006
		JP 2007501253 A	25-01-2007
		US 2005049209 A1	03-03-2005
		WO 2005016308 A1	24-02-2005
WO 2009124756 A1	15-10-2009	NONE	

PE2E SEARCH - Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
L1	17	(A61K9/1075 AND A61K9/0019 AND A61K31/43 AND A61K31/496 AND A61K31/5377 AND A61K47/10 AND A61K47/44)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/03/12 06:53 PM
L2	19	(A61K9/1075 AND A61K9/0019 AND A61K31/496 AND A61K31/5377 AND A61K47/10 AND A61K47/44)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/03/12 06:57 PM
L3	67	(A61K9/1075 AND A61K9/0019 AND A61K31/5377 AND A61K47/10 AND A61K47/44)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/03/12 06:58 PM
L4	1402	(A61K9/1075 AND A61K9/0019 AND A61K47/10 AND	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY,	OR	ON	ON	2024/03/12 06:58 PM

		A61K47/44)	CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)				
L5	31	((A61K9/1075 AND A61K9/0019 AND A61K47/10 AND A61K47/44) AND aprepitant)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/03/12 06:59 PM
L6	3999	(aprepitant AND phospholipid AND oil AND ethanol AND water AND inject$)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/03/12 07:02 PM
L7	31	((("Heron") near3 ("Therapeutics") near3 ("Inc"))).AS,AANM.	(USPAT)	OR	ON	ON	2024/03/12 07:17 PM

PE2E SEARCH - Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
N1	12	(A61K9/1075 AND A61K9/0019 AND A61K31/43 AND	(US-PGPUB; USPAT)	OR	ON	ON	2024/03/12 06:55 PM

		A61K31/496 AND A61K31/5377 AND A61K47/10 AND A61K47/44)					
N2	165	(A61K9/1075 AND A61K9/0019 AND A61K47/10 AND A61K47/44)	(US-PGPUB; USPAT)	OR	ON	ON	2024/03/12 06:59 PM
N3	11	((A61K9/1075 AND A61K9/0019 AND A61K47/10 AND A61K47/44) AND aprepitant)	(US-PGPUB; USPAT)	OR	ON	ON	2024/03/12 07:00 PM
N4	1154	(aprepitant AND phospholipid AND oil AND ethanol AND water AND inject$)	(US-PGPUB; USPAT)	OR	ON	ON	2024/03/12 07:03 PM

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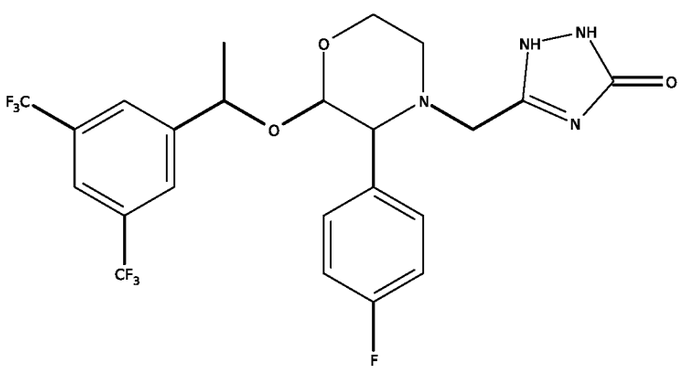
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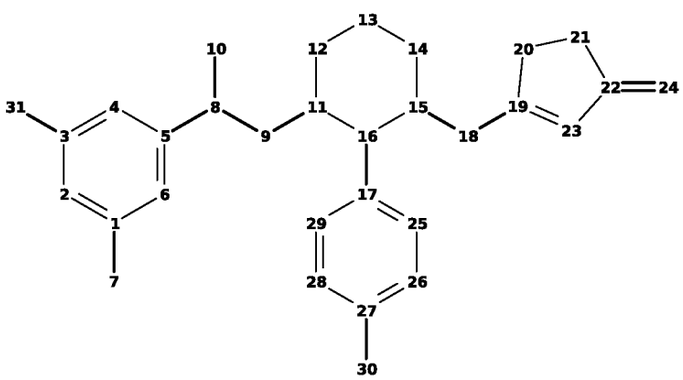
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Node Attributes
Ring Nodes : 1 2 3 4 5 6 11 12 13 14 15 16 17 19 22 23 25 26 27 28 29
Chain Nodes : 8 9 10 18 24 30
Bond Attributes
Ring Bonds : 1-2 2-3 3-4 4-5 5-6 6-1 11-12 12-13 13-14 14-15 15-16 16-11 17-25 19-20 20-21 21-22 22-23 23-19 25-26 26-27 27-28 28-29 29-17
Chain Bonds : 1-7 3-31 5-8 8-9 8-10 9-11 15-18 16-17 18-19 22-24 27-30
Exact Bonds : 1-7 3-31 5-8 8-10 16-17 18-19 27-30
Normalized Bonds : 1-2 2-3 3-4 4-5 5-6 6-1 17-25 25-26 26-27 27-28 28-29 29-17
Exact/Normalized Bonds : 8-9 9-11 11-12 12-13 13-14 14-15 15-16 15-18

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22  23  25  26  27  28  29
Match Level (CLASS) : 7  8  9  10  18  24  30  31
Element Count Level (LIMITED) : 1  2  3  4  5  6  7  8  9  10  11  12  13  14
15  16  17  18  19  20  21  22  23  24  25  26  27  28  29  30  31



L1      STRUCTURE UPLOADED

=> S L1 SSS FULL

FULL SEARCH INITIATED 15:59:31 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -      802 TO ITERATE

100.0% PROCESSED        802 ITERATIONS                                68 ANSWERS
SEARCH TIME: 00.00.01

L2           68 SEA SSS FUL L1

=> FILE CAPLUS

COST IN U.S. DOLLARS                          SINCE FILE           TOTAL
                                                   ENTRY         SESSION
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This file contains CAS Registry Numbers for easy and accurate
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=> S L2

L3         1679 L2

=> S L3 AND lecithin

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          62182 LECITHINS
          87410 LECITHIN
                (LECITHIN OR LECITHINS)
L4           48 L3 AND LECITHIN
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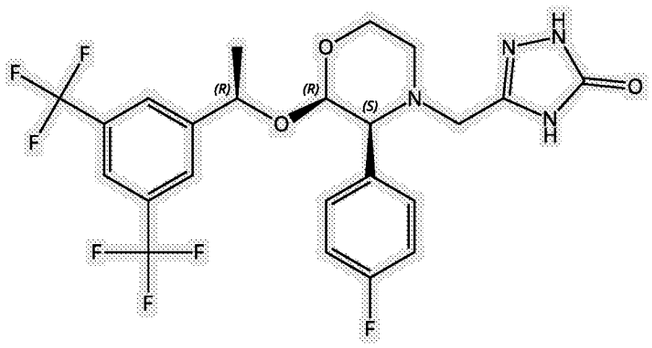
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=> S L4 AND emulsion

        426011 EMULSION
        262935 EMULSIONS
        526451 EMULSION
                 (EMULSION OR EMULSIONS)
L5          18 L4 AND EMULSION

=> D L5 1-18 IBIB ABS HITIND HITSTR


L5   ANSWER 1 OF 18  CAPLUS  COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER:        2024:141628  CAPLUS Full-text
TITLE:                   Aprepitant emulsion drug composition and preparation
                         method thereof
INVENTOR(S):             Chen, Xiangmei; Yu, Changhui; Wang, Xinlong; Lin,
                         Liyang; Shen, Li; Zhao, Dong
PATENT ASSIGNEE(S):      Sichuan Kelun Pharmaceutical Research Institute Co.,
                         Ltd., Peop. Rep. China
SOURCE:                  Faming Zhuanli Shenqing, 8pp.
                         CODEN: CNXXEV
DOCUMENT TYPE:           Patent
LANGUAGE:                Chinese
FAMILY ACC. NUM. COUNT:  1
PATENT INFORMATION:
     PATENT NO.          KIND  DATE        APPLICATION NO.         DATE
     ----------------    ----  --------    ---------------------   --------
     CN 117414334         A    20240119    CN 2022-10811953        20220711
PRIORITY APPLN. INFO.:                     CN 2022-10811953        20220711
PATENT STATUS PATENT INFORMATION:
     PATENT NO.          KIND  STATUS          STATUS DATE
     ----------------    ----  -------------   -----------
     CN 117414334         A    Alive           20240125
AB   The present invention provides an aprepitant emulsion drug compn. and
     prepn. method thereof, which has the advantages of high quality and good
     stability.  The method comprises the following steps: stirring and
     dissolving aprepitant, phospholipid, ethanol and soybean oil to obtain an
     oil phase, adding an isotonic regulator, the phospholipid and a pH
     regulator into water for injection, stirring uniformly to obtain a water
     phase, online shearing and mixing the oil phase and the water phase to
     prep. a primary emulsion, homogenizing by high-pressure microjet,
     sterilizing, filtering and filling.
IPCI A61K0009-107; A61K0031-5377; A61K0047-24; A61K0047-44; A61P0001-08
IPCR A61K0009-107 [I]; A61K0031-5377 [I]; A61K0047-24 [I]; A61K0047-44 [I];
     A61P0001-08 [I]
CC   63 (Pharmaceuticals)
ST   aprepitant emulsion drug prepn
IT   INDEXING IN PROGRESS
IT   Emulsions
     Filtration
     Mixing
     Sterilization and Disinfection
     Stirring
        (aprepitant emulsion drug compn. and prepn. method thereof)
IT   Egg yolk lecithins
     Soybean oil
     RL: MOA (Modifier or additive use); PEP (Physical, engineering or chemical
     process); THU (Therapeutic use); BIOL (Biological study); PROC (Process);
     USES (Uses)
        (aprepitant emulsion drug compn. and prepn. method thereof)
IT   64-17-5, Ethanol
     RL: MOA (Modifier or additive use); PEP (Physical, engineering or chemical
     process); THU (Therapeutic use); BIOL (Biological study); PROC (Process);
     USES (Uses)
        (aprepitant emulsion drug compn. and prepn. method thereof)
IT   57-50-1, D-Sucrose   143-19-1, Sodium oleate
     RL: PEP (Physical, engineering or chemical process); PROC (Process)
        (aprepitant emulsion drug compn. and prepn. method thereof)
IT   170729-80-3, Aprepitant
     RL: PEP (Physical, engineering or chemical process); THU (Therapeutic
     use); BIOL (Biological study); PROC (Process); USES (Uses)
        (aprepitant emulsion drug compn. and prepn. method thereof)
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IT 170729-80-3, Aprepitant
RL: PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(aprepitant emulsion drug compn. and prepn. method thereof)
RN 170729-80-3 CAPLUS
CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
CN 117414334 A	CN 2022-10811953	Register|Global Dossier

L5 ANSWER 2 OF 18 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2022:1355958 CAPLUS Full-text
DOCUMENT NUMBER: 179:75293
TITLE: Stable antiemetic emulsions
INVENTOR(S): Bhagwatwar, Harshal Prabhakar; Nerurkar, Manoj
PATENT ASSIGNEE(S): Steps BioSciences, Inc., USA
ULTIMATE OWNER: STEPS BIOSCIENCES
ULTIMATE OWNER STANDARD: STEPS BIOSCIENCES
SOURCE: U.S. Pat. Appl. Publ., 11pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

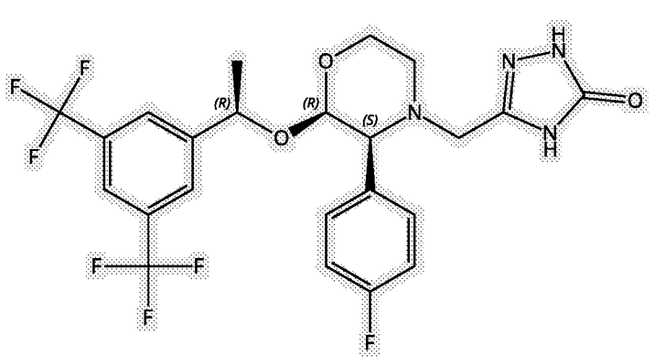
PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 20220160722	A1	20220526	US 2021-17531216		20211119
PRIORITY APPLN. INFO.:			IN 2020-41050531	A	20201120

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
US 20220160722	A1	Alive	20220609

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASFORMULTNS 2022:1355958
AB Emulsion formulations and systems for the i.v. or parenteral administration. of neurokinin-1 (NK-1) receptor antagonists for treatment of emesis are provided. Methods for prepg. the stable NK-1 receptor antagonist emulsions and pharmaceutical formulations are further provided. The emulsion formulations are prepd. and characterized as a formulation and process that will allow an NK-1 receptor antagonist compd. to be incorporated into an emulsion for i.v. injection and remain stable during the shelf life of the formulation. Specifically, emulsion formulations have an oil phase that includes oil, ethanol, egg lecithin , and the further addn. of sodium oleate that is mixed with an aq. phase and processed to form the emulsion formulation.
IPCI A61K0031-5377 [I]; A61K0009-00 [I]; A61K0009-107 [I]; A61K0047-24 [I];

A61K0047-12 [I]; A61K0047-10 [I]; A61K0047-44 [I]
IPCR A61K0031-5377 [I]; A61K0009-00 [I]; A61K0009-107 [I]; A61K0047-10 [I];
A61K0047-12 [I]; A61K0047-24 [I]; A61K0047-44 [I]
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1
ST antiemetic emulsion neurokinin receptor antagonist
IT Antiemetics
Buffers
Emulsifying agents
Neurokinin 1 receptor antagonists
Parenteral drug delivery systems
Pharmaceutical dispersions
Pharmaceutical emulsions
Pharmaceutical formulations
Pharmaceutical injections
Pharmaceutical intravenous injections
Pharmaceutical tonicity modifiers
Stability
Vomiting
Zeta potential
pH
(stable antiemetic emulsions)
IT Castor oil
Coconut oil
Corn oil
Cottonseed oil
Egg yolk lecithins
Lecithins
Olive oil
Safflower oil
Sesame oil
Soybean oil
Triglycerides
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(stable antiemetic emulsions)
IT 57-50-1, Sucrose, biological studies 64-17-5, Ethanol, biological
studies 111-62-6, Ethyl oleate 143-19-1, Sodium oleate 303-43-5,
Cholesteryl oleate 544-35-4, Ethyl linoleate 604-33-1, Cholesteryl
linoleate 37220-82-9, Glyceryl oleate 37348-65-5, Glyceryl linoleate
136745-48-7, Octyl glycerate 152167-64-1, Decyl glycerate
170729-80-3, Aprepitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(stable antiemetic emulsions)
IT 170729-80-3, Aprepitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(stable antiemetic emulsions)
RN 170729-80-3 CAPLUS
CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phen
yl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX
NAME)



Absolute stereochemistry shown
Rotation (+)

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
US 20220160722 A1	US 2021-17531216	Register|Global Dossier

L5 ANSWER 3 OF 18 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2022:139737 CAPLUS Full-text
DOCUMENT NUMBER: 177:284905
TITLE: Pharmaceutical emulsion comprising an aprepitant, pharmaceutical injections, and methods of preparing emulsions
INVENTOR(S): Amano, Yohei; Katagiri, Kazumi
PATENT ASSIGNEE(S): Kewpie Corporation, Japan; FBC (Shanghai) Pharmaceutical Technology Co., Ltd.
ULTIMATE OWNER: FBC SHANGHAI PHARMACEUTICAL TECHNOLOGY; FBC SHANGHAI PHARMACEUTICAL TECH; FUBICHENG SHANGHAI MEDICAL TECH; KEWPIE CORPORATION
ULTIMATE OWNER STANDARD: FBC SHANGHAI PHARMACEUTICAL TECHNOLOGY; FBC SHANGHAI PHARMACEUTICAL TECH; FUBICHENG SHANGHAI MEDICAL TECH; Kewpie Corp
SOURCE: PCT Int. Appl., 28pp.; Chemical Indexing Equivalent to 174:540291 (JP)
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2022014113	A1	20220120	WO 2021-JP15552		20210415
JP 6832468	B1	20210224	JP 2020-121438		20200715
JP 2022018370	A	20220127			
CA 3187858	A1	20220120	CA 2021-3187858		20210415
KR 2023040956	A	20230323	KR 2022-7045138		20210415
EP 4169515	A1	20230426	EP 2021-843280		20210415
US 20230310443	A1	20231005	US 2023-18015492		20230110
PRIORITY APPLN. INFO.:			JP 2020-121438	A	20200715
			WO 2021-JP15552	W	20210415

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
WO 2022014113	A1	Alive	20220203
JP 6832468	B1	Alive	20210304
JP 2022018370	A	Alive	20220224
CA 3187858	A1	Alive	20230216
KR 2023040956	A	Alive	20230420
EP 4169515	A1	Alive	20230427
US 20230310443	A1	Alive	20231012

AB The present invention pertains to an emulsion which contains an aprepitant, an emulsifier, an oil, a polyethylene glycol having an av. mol. wt. of 260-1100, and water, and to which ethanol is substantially not added. The content of the aprepitant is 0.50-0.90 w/v% based on the total amt., and the content of the emulsifier is 12.0-18 w/v%. The content of oil is 7.0-12.0 w/v %, and the content of polyethylene glycol is 0.5-10.0 w/v %. The av. particle diam. of the emulsion is 60-140 nm. According to the present invention, provided is an aprepitant-contg. emulsion having excellent stability without substantially adding ethanol.
IPCI A61K0031-5377 [I]; A61K0009-107 [I]; A61K0047-10 [I]; A61K0047-24 [I]; A61K0047-44 [I]; A61P0001-08 [I]
IPCR A61K0031-5377 [I]; A61K0009-107 [I]; A61K0047-10 [I]; A61K0047-24 [I]; A61K0047-44 [I]; A61P0001-08 [I]
CC 63-6 (Pharmaceuticals)
ST aprepitant pharmaceutical emulsion injection
IT Emulsifying agents
Pharmaceutical emulsions
Pharmaceutical injections
Tonicity modifiers
(pharmaceutical emulsion comprising aprepitant, pharmaceutical injections, and methods of prepg. emulsions)
IT Egg yolk lecithins
Phospholipids

Polyoxyalkylenes
Soybean oil
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical emulsion comprising aprepitant, pharmaceutical injections, and methods of prepg. emulsions)

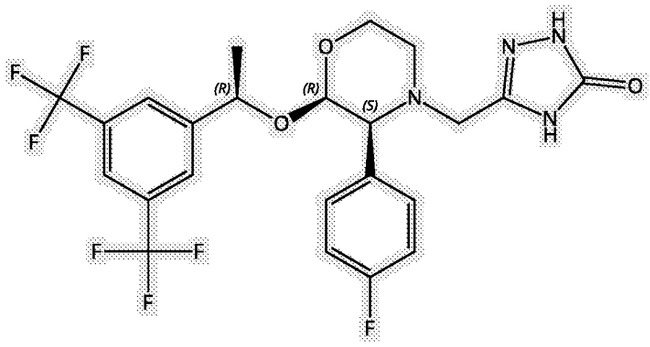
IT 170729-80-3
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical emulsion comprising aprepitant, pharmaceutical injections, and methods of prepg. emulsions)

IT 57-50-1, biological studies 112-80-1, 9-Octadecenoic acid (9Z)-, biological studies 143-19-1 25322-68-3
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical emulsion comprising aprepitant, pharmaceutical injections, and methods of prepg. emulsions)

IT 170729-80-3
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical emulsion comprising aprepitant, pharmaceutical injections, and methods of prepg. emulsions)

RN 170729-80-3 CAPLUS

CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
CA 3187858 A1	CA 2021-3187858	Register
EP 4169515 A1	EP 2021-843280	Register|Federated Reg.
JP 2022018370 A	JP 2020-121438	Register|Global Dossier
JP 6832468 B1	JP 2020-121438	Register|Global Dossier
KR 2023040956 A	KR 2022-7045138	Register|Global Dossier
US 20230310443 A1	US 2023-18015492	Register|Global Dossier
WO 2022014113 A1	WO 2021-JP15552	Register|Global Dossier

L5 ANSWER 4 OF 18 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2021:2591917 CAPLUS Full-text
DOCUMENT NUMBER: 177:123225
TITLE: Preparation method of aprepitant emulsion injection for preventing nausea and emesis
INVENTOR(S): Guo, Shuer; Qin, Zhijun
PATENT ASSIGNEE(S): Guangzhou Manxiang Pharmaceutical Co., Ltd., Peop. Rep. China
ULTIMATE OWNER: GUANGZHOU MAXENMED MEDICINE
ULTIMATE OWNER STANDARD: GUANGZHOU MAXENMED MEDICINE
SOURCE: Faming Zhuanli Shenqing, 9pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

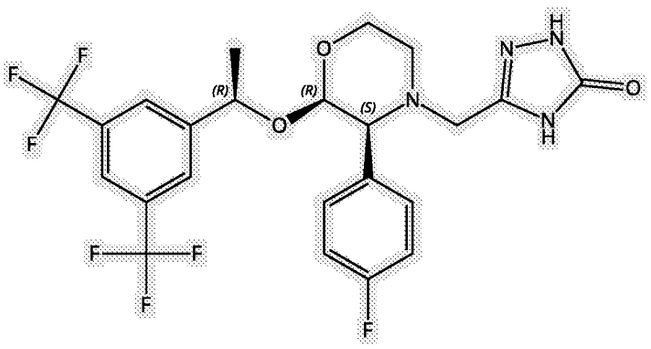
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 113712915	A	20211130	CN 2021-10018100	20210107

PRIORITY APPLN. INFO.: CN 2021-10018100 20210107
PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
CN 113712915	A	Alive	20211209

OTHER SOURCE(S): CASFORMULTNS 2021:2591917
AB The invention aprepitant emulsion injection is prepd. from (by wt%) aprepitant 0.2-1.2, pH regulator 0.25-0.75, permeation pressure regulator 3-8, injection water 56-75, emulsifier 12-15, cosolvent 2-5, and injection oil 5-15. The emulsifier is hydrogenated soybean lecithin or hydrogenated soybean phosphatidylcholine. The pH regulator is sodium hydroxide, sodium citrate, sodium dihydrogen phosphate or sodium oleate. The permeation pressure regulator is xylitol, sorbitol, mannitol or sucrose. The cosolvent is ethanol, glycerol, propylene glycol and polyethylene glycol. The injection oil is soybean oil, peanut oil, hydrogenated corn oil, triglyceride, medium-chain triglyceride, sesame oil and/or sunflower seed oil. By controlling content of emulsifier and shearing rotation speed, homogenization pressure and homogenization temp. in emulsion prepn. process, the invention preps. aprepitant emulsion injection with good oxidn. resistance and emulsification effect, and has operability, simple process and low device loss.
IPCI A61K0009-107; A61K0047-24; A61K0031-5377; A61P0001-08; A61P0035-00
IPCR A61K0009-107 [I]; A61K0031-5377 [I]; A61K0047-24 [I]; A61P0001-08 [I]; A61P0035-00 [I]
CC 63-6 (Pharmaceuticals)
ST aprepitant emulsion injection nausea emesis
IT Corn oil
Soya lecithins
RL: MOA (Modifier or additive use); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hydrogenated; prepn. method of aprepitant emulsion injection for preventing nausea and emesis)
IT Antiemetics
Biological permeation
Cosolvents
Emulsifying agents
Homo sapiens
Homogenization
Human
Nausea
Pharmaceutical emulsions
Pharmaceutical injections
Vomiting
pH
(prepn. method of aprepitant emulsion injection for preventing nausea and emesis)
IT Hydrogenated soya phosphatidylcholines
Medium-chain glycerides
Oils
Peanut oil
Polyoxyalkylenes
Sesame oil
Soybean oil
Sunflower oil
Triglycerides
RL: MOA (Modifier or additive use); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. method of aprepitant emulsion injection for preventing nausea and emesis)
IT 50-70-4, Sorbitol, biological studies 56-81-5, Glycerol, biological studies 57-50-1, Sucrose, biological studies 57-55-6, Propylene glycol, biological studies 64-17-5, Ethanol, biological studies 68-04-2 69-65-8, D-Mannitol 87-99-0, Xylitol 143-19-1, Sodium oleate 1310-73-2, Sodium hydroxide, biological studies 7558-80-7, Sodium dihydrogen phosphate 25322-68-3, Polyethylene glycol
RL: MOA (Modifier or additive use); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(prepn. method of aprepitant emulsion injection for
preventing nausea and emesis)
IT 170729-80-3, Aprepitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. method of aprepitant emulsion injection for
preventing nausea and emesis)
IT 170729-80-3, Aprepitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. method of aprepitant emulsion injection for
preventing nausea and emesis)
RN 170729-80-3 CAPLUS
CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phen
yl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX
NAME)



Absolute stereochemistry shown
Rotation (+)

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
CN 113712915 A	CN 2021-10018100	Register|Global Dossier

L5 ANSWER 5 OF 18 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2021:1541826 CAPLUS Full-text
DOCUMENT NUMBER: 175:329880
TITLE: Aprepitant ready-to-use injection emulsion compositions
INVENTOR(S): Akasapu, Prem Sagar; Subramanian, Veerappan; Subramanian, Ilango
PATENT ASSIGNEE(S): Somerset Therapeutics LLC, USA
ULTIMATE OWNER: SOMERSET THERAPEUTICS LLC
ULTIMATE OWNER STANDARD: SOMERSET THERAPEUTICS LLC
SOURCE: U.S. Pat. Appl. Publ., 8pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20210212933	A1	20210715	US 2021-17147556	20210113
US 11517522	B2	20221206		

PRIORITY APPLN. INFO.: US 2020-62961039 P 20200114
PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
US 20210212933	A1	Alive	20210722
US 11517522	B2	Alive	20221215

OTHER SOURCE(S): CASFORMULTNS 2021:1541826
AB The present invention provides an emulsion compn. comprising aprepitant for treatment of emesis. Particularly, the invention is a ready-to-use emulsion compns. comprising aprepitant and medium chain triglycerides

for administration by i.v. infusion, wherein the emulsion compn. is also free of ethanol. Further, the invention also provides processes of prepg. such compns. and their use for the prevention and control of acute and delayed chemotherapy-induced nausea and vomiting, and/or for prevention of postoperative nausea and vomiting.

IPCI A61K0009-00 [I]; A61K0009-107 [I]; A61K0047-14 [I]; A61M0005-24 [I]; A61K0031-5377 [I]; A61K0009-00 [I]; A61K0047-14 [I]; A61K0009-107 [I]; A61K0031-5377 [I]; A61M0005-24 [I]

IPCR A61K0009-00 [I]; A61K0009-107 [I]; A61K0031-5377 [I]; A61K0047-14 [I]; A61M0005-24 [I]

CC 63-6 (Pharmaceuticals)

ST aprepitant injection emulsion

IT Humidity
Nausea
Oil-in-water emulsions
Pharmaceutical emulsions
Pharmaceutical intravenous infusions
Vomiting
Zeta potential
pH
(aprepitant ready-to-use injection emulsion compns.)

IT Lecithins
Medium-chain glycerides
Polyoxyalkylenes
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aprepitant ready-to-use injection emulsion compns.)

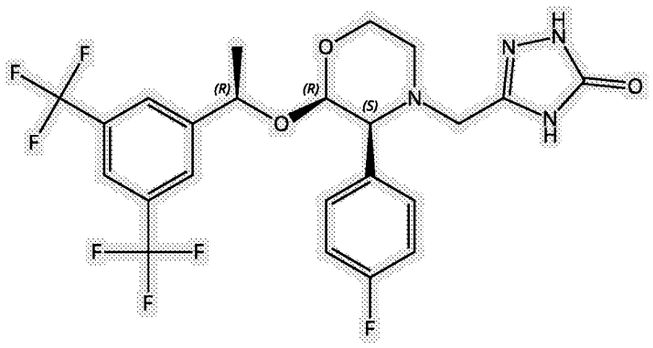
IT 170729-80-3, Aprepitant
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aprepitant ready-to-use injection emulsion compns.)

IT 50-70-4, Sorbitol, biological studies 50-99-7, Dextrose, biological studies 56-81-5, Glycerol, biological studies 57-50-1, Sucrose, biological studies 57-55-6, Propylene glycol, biological studies 63-42-3, Lactose 64-17-5, Ethanol, biological studies 69-65-8, Mannitol 69-79-4, Maltose 87-99-0, Xylitol 99-20-7, Trehalose 512-69-6, Raffinose 7647-14-5, Sodium chloride, biological studies 9004-54-0, Dextran, biological studies 25322-68-3, Poly ethylene glycol
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aprepitant ready-to-use injection emulsion compns.)

IT 170729-80-3, Aprepitant
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aprepitant ready-to-use injection emulsion compns.)

RN 170729-80-3 CAPLUS

CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

LINK INFORMATION
PUBLICATIONS APPLICATIONS REGISTER

US 11517522 B2	US 2021-17147556	Register|Global Dossier
US 20210212933 A1	US 2021-17147556	Register|Global Dossier

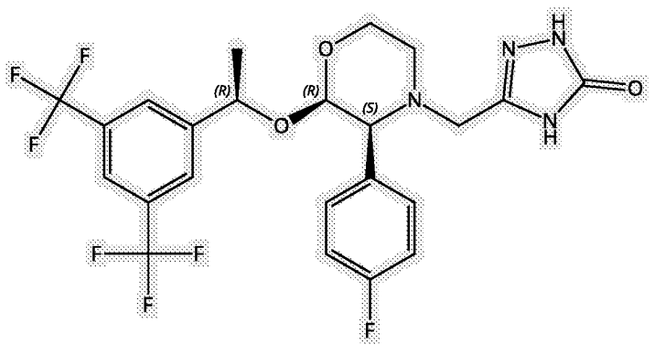
L5 ANSWER 6 OF 18 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2021:685825 CAPLUS Full-text
DOCUMENT NUMBER: 178:140851
TITLE: Aprepitant submicroemulsion injection capable of being autoclaved, and its preparation method
INVENTOR(S): Qin, Linghao; Li, Yusheng; Zhu, Wanye; Wang, Wanting
PATENT ASSIGNEE(S): Guangdong Pharmaceutical University, Peop. Rep. China
SOURCE: Faming Zhuanli Shenqing, 19pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 112535661	A	20210323	CN 2020-11524237	20201222
CN 112535661	B	20230407		

PRIORITY APPLN. INFO.: CN 2020-11524237 20201222
PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
CN 112535661	A	Alive	20210408
CN 112535661	B	Alive	20230427

OTHER SOURCE(S): CASFORMULTNS 2021:685825
AB A safe aprepitant submicroemulsion injection capable of being autoclaved having high efficiency, good stability and sterilization effect, and wide application in medicine field is provided. The aprepitant submicroemulsion injection comprises: polyethylene glycol 15hydroxystearate, phospholipids, aprepitant, oil for injection, emulsifier, co-emulsifier, solubilizer, stabilizer, isotonic agent, pH regulator and water for injection. The prepn. method comprises the following steps: (1) mixing aprepitant, injection oil and solubilizer, dissolving and dispersing with alc., and removing the alc. to obtain an oil phase mixt.; (2) stirring and mixing the emulsifier, co-emulsifier, stabilizer, isotonic agent and water for injection, and heat to dissolve to obtain the water phase mixt.; and (3) adding the oil phase mixt. to the water phase mixt., prepg. the emulsion , and autoclaving to obtain the aprepitant submicroemulsion injection. The aprepitant submicroemulsion injection is used in the prepn. of a medicine for treating nausea and vomiting.
IPCI A61K0009-107; A61K0031-5377; A61K0047-24; A61K0047-14; A61K0047-18; A61P0001-08; A61L0002-07
IPCR A61K0009-107 [I]; A61K0031-5377 [I]; A61K0047-14 [I]; A61K0047-18 [I]; A61K0047-24 [I]; A61L0002-07 [I]; A61P0001-08 [I]
CC 63-6 (Pharmaceuticals)
IT Amino acids
Egg yolk lecithins
Oils
Phospholipids
RL: MOA (Modifier or additive use); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aprepitant submicroemulsion injection capable of being autoclaved, and its prepn. method)
IT 56-41-7, L-Alanine, biological studies 56-84-8, L-Aspartic acid, biological studies 56-86-0, L-Glutamic acid, biological studies 63-91-2, L-Phenylalanine, biological studies 73-32-5, L-Isoleucine, biological studies 170729-80-3, Aprepitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aprepitant submicroemulsion injection capable of being autoclaved, and its prepn. method)
IT 170729-80-3, Aprepitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aprepitant submicroemulsion injection capable of being autoclaved, and its prepn. method)
RN 170729-80-3 CAPLUS
CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
CN 112535661 A	CN 2020-11524237	Register|Global Dossier
CN 112535661 B	CN 2020-11524237	Register|Global Dossier

L5 ANSWER 7 OF 18 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2021:481715 CAPLUS Full-text
DOCUMENT NUMBER: 174:540291
TITLE: Pharmaceutical emulsion comprising an aprepitant, pharmaceutical injections, and methods of preparing emulsions
INVENTOR(S): Amano, Yohei; Katagiri, Kazumi
PATENT ASSIGNEE(S): Kewpie Corporation, Japan; FBC (Shanghai) Pharmaceutical Technology Co., Ltd.
ULTIMATE OWNER: KEWPIE CORPORATION; FBC SHANGHAI PHARMACEUTICAL TECH; FUBICHENG SHANGHAI MEDICAL TECH; FBC SHANGHAI PHARMACEUTICAL TECHNOLOGY
ULTIMATE OWNER STANDARD: Kewpie Corp; FBC SHANGHAI PHARMACEUTICAL TECH; FUBICHENG SHANGHAI MEDICAL TECH; FBC SHANGHAI PHARMACEUTICAL TECHNOLOGY
SOURCE: Jpn. Tokkyo Koho, 15pp.; Chemical Indexing Equivalent to 177:284905 (WO)
CODEN: JTXXFF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 6832468	B1	20210224	JP 2020-121438	20200715
JP 2022018370	A	20220127		
CA 3187858	A1	20220120	CA 2021-3187858	20210415
WO 2022014113	A1	20220120	WO 2021-JP15552	20210415
KR 2023040956	A	20230323	KR 2022-7045138	20210415
EP 4169515	A1	20230426	EP 2021-843280	20210415
CN 113952299	A	20220121	CN 2021-10772526	20210708
CN 117017915	A	20231110	CN 2023-11089804	20210708
US 20230310443	A1	20231005	US 2023-18015492	20230110

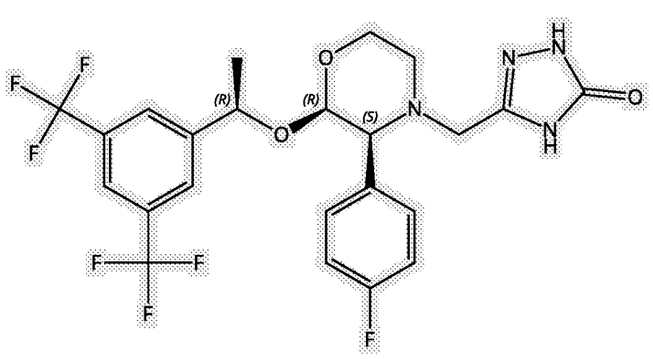
PRIORITY APPLN. INFO.:

JP 2020-121438	A	20200715
WO 2021-JP15552	W	20210415
CN 2021-10772526	A3	20210708

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
JP 6832468	B1	Alive	20210304
JP 2022018370	A	Alive	20220224
CA 3187858	A1	Alive	20230216
WO 2022014113	A1	Alive	20220203

KR 2023040956 A Alive 20230420
EP 4169515 A1 Alive 20230427
CN 113952299 A Alive 20220203
CN 117017915 A Alive 20231116
US 20230310443 A1 Alive 20231012
OTHER SOURCE(S): CASFORMULTNS 2021:481715
AB The emulsion comprises: an aprepitant, an emulsifier, an oil, polyethylene glycol and water, with substantially no addn. of ethanol. The emulsion comprises a pH regulator and having a pH of 8.0-9.0. The content of the aprepitant is 0.50 w/v% or more and 0.90 w/v% or less based on the total amt., and the content of the emulsifier is 12.0 w/v% or more and 12.0 w/v% or more based on the total amt. The emulsion is 0 w/v% or less, the emulsion in which the emulsifier is a phospholipid. According to the present invention, provided is an aprepitant-contg. emulsion having excellent stability without substantially adding ethanol.
IPCI A61K0031-5377 [I]; A61K0009-107 [I]; A61P0001-08 [I]; A61K0047-10 [I]; A61K0047-24 [I]; A61K0047-44 [I]; A61K0009-107 [I]; A61K0047-10 [I]; A61K0031-5377 [I]; A61P0001-08 [I]; A61K0047-24 [I]; A61K0047-44 [I]
IPCR A61K0031-5377 [I]; A61K0009-107 [I]; A61K0047-10 [I]; A61K0047-24 [I]; A61K0047-44 [I]; A61P0001-08 [I]
CC 63-6 (Pharmaceuticals)
ST aprepitant pharmaceutical emulsion injection
IT Emulsifying agents
Pharmaceutical emulsions
Pharmaceutical injections
Tonicity modifiers
(pharmaceutical emulsion comprising aprepitant, pharmaceutical injections, and methods of prepg. emulsions)
IT Egg yolk lecithins
Phospholipids
Polyoxyalkylenes
Soybean oil
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical emulsion comprising aprepitant, pharmaceutical injections, and methods of prepg. emulsions)
IT 170729-80-3
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical emulsion comprising aprepitant, pharmaceutical injections, and methods of prepg. emulsions)
IT 57-50-1, biological studies 112-80-1, 9-Octadecenoic acid (9Z)-, biological studies 143-19-1 25322-68-3
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical emulsion comprising aprepitant, pharmaceutical injections, and methods of prepg. emulsions)
IT 170729-80-3
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical emulsion comprising aprepitant, pharmaceutical injections, and methods of prepg. emulsions)
RN 170729-80-3 CAPLUS
CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
CA 3187858 A1	CA 2021-3187858	Register
CN 113952299 A	CN 2021-10772526	Register|Global Dossier
CN 117017915 A	CN 2023-11089804	Register|Global Dossier
EP 4169515 A1	EP 2021-843280	Register|Federated Reg.
JP 2022018370 A	JP 2020-121438	Register|Global Dossier
JP 6832468 B1	JP 2020-121438	Register|Global Dossier
KR 2023040956 A	KR 2022-7045138	Register|Global Dossier
US 20230310443 A1	US 2023-18015492	Register|Global Dossier
WO 2022014113 A1	WO 2021-JP15552	Register|Global Dossier

L5 ANSWER 8 OF 18 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2020:485442 CAPLUS Full-text
DOCUMENT NUMBER: 177:51750
TITLE: Aprepitant Intravenous Emulsion Based on Ion Pairing/Phospholipid Complex for Improving Physical and Chemical Stability During Thermal Sterilization
AUTHOR(S): Zhang, Xinyu; Wei, Ying; Cao, Zhijun; Xu, Ying; Lu, Cong; Zhao, Meiqi; Gou, Jingxin; Yin, Tian; Zhang, Yu; He, Haibing; Wang, Yanjiao; Tang, Xing
CORPORATE SOURCE: Department of Pharmaceutics, Shenyang Pharmaceutical University, Shenyang, Peop. Rep. China
SOURCE: AAPS PharmSciTech (2020), 21(3), 75
CODEN: AAPHFZ; ISSN: 1530-9932
DIGITAL OBJECT ID: 10.1208/s12249-019-1605-7
PUBLISHER: Springer
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English

AB An aprepitant (APT) cholesteryl hemisuccinate (CHEMS) ion pair complex emulsion (AIPE) with high lecithin content was prepd. to improve sterilization stability through the film dispersion homogenization method; therefore, it could be a promising delivery system of APT. Medium-chain triglycerides (MCT) was selected as the oil phase to improve the soly. and stability of APT in oil phase. DSC, XRD, FT-IR, and 1H-NMR spectroscopies confirmed that the APT-CHEMS ion pair (AIP) was formed between CHEMS and APT. The formation of AIP significantly increased the hydrophobicity of APT, allowing it to be completely embedded in the oil phase core to improve chem. stability and decrease hydrolysis of APT in the water phase. Also, CHEMS had a strong affinity with lecithin and could stabilize lipid membranes, forming a stronger and thicker interface membrane to increase the phys. stability of AIPE. As a result, AIPE could withstand autoclaving at 120°C for 8 min without any change of particle size or content. Furthermore, AIPE with a potential of - 53.4 mV remained stable through spatial repulsion during sterilization. The encapsulation efficiency of AIPE was over 90% and the particle size was 106.8 ± 65.62 nm(0.286). Pharmacokinetic study in rats was comparable with that of CINVANTI which yielded a relative bioavailability of 114.31% indicating that the AIPE had similar pharmacokinetic processes in vivo with the analog of CINVANTI. The AUC0-t of the AIPE was 4.31-fold that of the APT soln.

CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1
ST aprepitant intravenous emulsion ion pairing phospholipid stability thermal sterilization
IT Chemical stability
Dissolution
Drug bioavailability
Encapsulation
Hydrolysis
Hydrophobicity
Ion pairs
Lipophilicity
Particle size distribution
Pharmaceutical emulsions
Pharmaceutical intravenous injections
Pharmacokinetics
Solubility

Surface structure
Thermal stability
Thermal sterilization
Zeta potential
(aprepitant i.v. emulsion based on ion pairing/phospholipid complex for improving phys. and chem. stability during thermal sterilization)

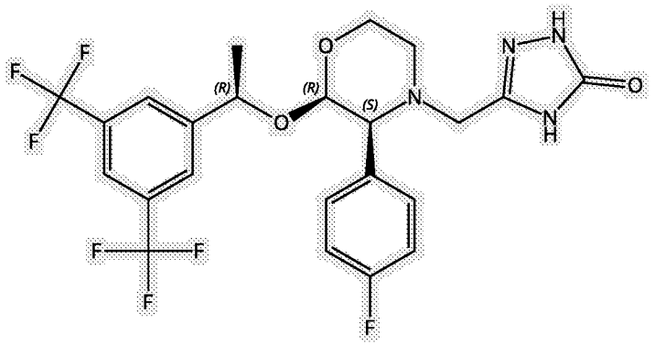
IT Egg yolk lecithins
Medium-chain glycerides
Soya lecithins
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aprepitant i.v. emulsion based on ion pairing/phospholipid complex for improving phys. and chem. stability during thermal sterilization)

IT 1510-21-0
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aprepitant i.v. emulsion based on ion pairing/phospholipid complex for improving phys. and chem. stability during thermal sterilization)

IT 170729-80-3
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aprepitant i.v. emulsion based on ion pairing/phospholipid complex for improving phys. and chem. stability during thermal sterilization)

IT 170729-80-3
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aprepitant i.v. emulsion based on ion pairing/phospholipid complex for improving phys. and chem. stability during thermal sterilization)

RN 170729-80-3 CAPLUS
CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

OS.CITING REF COUNT: 6 THERE ARE 6 CAPLUS RECORDS THAT CITE THIS RECORD (6 CITINGS)
REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 9 OF 18 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2020:245679 CAPLUS Full-text
DOCUMENT NUMBER: 172:258881
TITLE: Emulsion containing high proportion emulsifier and preparation method thereof
INVENTOR(S): Niu, Yawei; Xu, Wendong; Tang, Shunzhi; Yuan, Cheng; Fu, Yuping; Guan, Weijian; Wang, Guocai; Mou, Xiaonan; Li, Jirong; Li, Yao

PATENT ASSIGNEE(S): Guangzhou Baiyunshan Hanfang Pharmaceutical Co., Ltd., Peop. Rep. China
ULTIMATE OWNER: GUANGZHOU BAIYUNSHAN PHARMACEUTICAL HOLDINGS CO., LTD.
ULTIMATE OWNER STANDARD: Guangzhou Baiyunshan Pharma
SOURCE: Faming Zhuanli Shenqing, 15pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

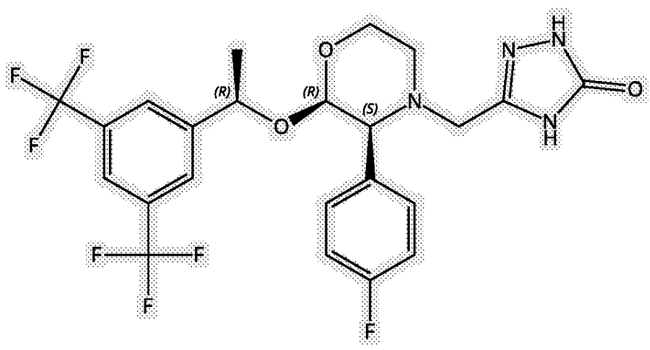
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 110772482	A	20200211	CN 2019-11215436	20191202

PRIORITY APPLN. INFO.: CN 2019-11215436 20191202
PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
CN 110772482	A	Dead	20230511

AB The invention discloses an emulsion contg. high proportion emulsifier and prepn. method thereof, which has the advantages of high drug loading and high bioavailability. The emulsion contg. high proportion emulsifier comprises the following raw materials in percentage by wt.: oil phase solvent 10-30%, emulsifier 10-30%, co-emulsifier 1-5%, volatile assistant 1-5%, stabilizer 0.05-0.6%, isoosmotic adjusting agent 1-5%, viscosity regulator 1-10%, active pharmaceutical ingredient 1-5%, and the balance of injection water.
IPCI A61K0009-107; A61K0047-26; A61K0047-44; A61K0047-14; A61K0047-10; A61K0031-5377
IPCR A61K0009-107 [I]; A61K0031-5377 [I]; A61K0047-10 [I]; A61K0047-14 [I]; A61K0047-26 [I]; A61K0047-44 [I]
CC 63-7 (Pharmaceuticals)
ST emulsifier emulsion
IT Glycerides
RL: MOA (Modifier or additive use); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(C8-10; emulsion contg. high proportion emulsifier and prepn. method thereof)
IT Emulsifying agents
Oilseed
Pharmaceutical emulsions
(emulsion contg. high proportion emulsifier and prepn. method thereof)
IT Carbohydrates
Castor oil
Egg yolk lecithins
Fish oil
Fructooligosaccharides
Olive oil
Phosphatidylcholines
Phosphatidylglycerols
Soya lecithins
Soybean oil
Triglycerides
RL: MOA (Modifier or additive use); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(emulsion contg. high proportion emulsifier and prepn. method thereof)
IT Camellia
Coix
(seed oil; emulsion contg. high proportion emulsifier and prepn. method thereof)
IT 9005-63-4D, fatty acid ester
RL: MOA (Modifier or additive use); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(Polysorbate; emulsion contg. high proportion emulsifier and prepn. method thereof)
IT 56-81-5, Glycerol, biological studies 57-48-7, D-Fructose, biological studies 57-50-1, D-Sucrose, biological studies 57-55-6, Propylene glycol, biological studies 64-17-5, Ethanol, biological studies 69-65-8, D-Mannitol 69-79-4, D-Maltose 87-79-6, L-Sorbose 112-80-1, Oleic acid, biological studies 143-19-1, Sodium oleate 538-23-8, Glycerin tricaprylate 538-24-9, Glycerol trilaurate 621-71-6, Glycerol

tridecanoate 106392-12-5, Poloxamer
RL: MOA (Modifier or additive use); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(emulsion contg. high proportion emulsifier and prepn. method thereof)
IT 170729-80-3, Aprepitant 552292-08-7, Rolapitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(emulsion contg. high proportion emulsifier and prepn. method thereof)
IT 170729-80-3, Aprepitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(emulsion contg. high proportion emulsifier and prepn. method thereof)
RN 170729-80-3 CAPLUS
CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
CN 110772482 A	CN 2019-11215436	Register|Global Dossier

L5 ANSWER 10 OF 18 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2019:1475315 CAPLUS Full-text
DOCUMENT NUMBER: 171:221789
TITLE: Method of administering emulsion formulations of an NK-1 receptor antagonist
INVENTOR(S): Ottoboni, Thomas B.; Quart, Barry D.
PATENT ASSIGNEE(S): Heron Therapeutics, Inc., USA
ULTIMATE OWNER: HERON THERAPEUTICS, INC.
ULTIMATE OWNER STANDARD: HERON THERAPEUTICS, INC.
SOURCE: U.S. Pat. Appl. Publ., 23pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 20190231688	A1	20190801	US 2019-16261459		20190129
WO 2019152430	A1	20190808	WO 2019-US15708		20190129
AU 2019214872	A1	20200806	AU 2019-214872		20190129
EP 3746051	A1	20201209	EP 2019-705044		20190129
JP 2021512091	T	20210513	JP 2020-541556		20190129
PRIORITY APPLN. INFO.:			US 2018-62624050	P	20180130
			WO 2019-US15708	W	20190129

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
US 20190231688	A1	Alive	20230914
WO 2019152430	A1	Dead	20220929
AU 2019214872	A1	Dead	20230803
EP 3746051	A1	Dead	20211117
JP 2021512091	T	Alive	20210520

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OTHER SOURCE(S): CASFORMULTNS 2019:1475315

AB Disclosed herein are methods of administering pharmaceutical formulations of a neurokinin-1 (NK-1) receptor antagonist to a subject in need of treatment of emesis.

IPCI A61K0009-107 [I]; A61K0031-5377 [I]; A61K0009-00 [I]; A61K0047-24 [I]; A61K0031-573 [I]; A61K0047-44 [I]; A61K0047-10 [I]; A61K0047-12 [I]; A61K0047-26 [I]; A61K0031-496 [I]

IPCR A61K0009-107 [I]; A61K0009-00 [I]; A61K0031-496 [I]; A61K0031-5377 [I]; A61K0031-573 [I]; A61K0047-10 [I]; A61K0047-12 [I]; A61K0047-24 [I]; A61K0047-26 [I]; A61K0047-44 [I]

CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1, 2

ST NK1 receptor antagonist dexamethasone emulsion administering method antiemetics

IT Surfactants
(co-; method of administering emulsion formulations of NK-1 receptor antagonist)

IT Antitumor agents
(emetogenic; method of administering emulsion formulations of NK-1 receptor antagonist)

IT Antiemetics
Emulsifying agents
Homo sapiens
Human
Nausea
Neurokinin 1 receptor antagonists
Pharmaceutical emulsions
Pharmaceutical intravenous injections
Pharmaceutical tonicity modifiers
Vomiting
pH-adjusting agents
(method of administering emulsion formulations of NK-1 receptor antagonist)

IT Alcohols
Egg yolk lecithins
Phospholipids
Soybean oil
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(method of administering emulsion formulations of NK-1 receptor antagonist)

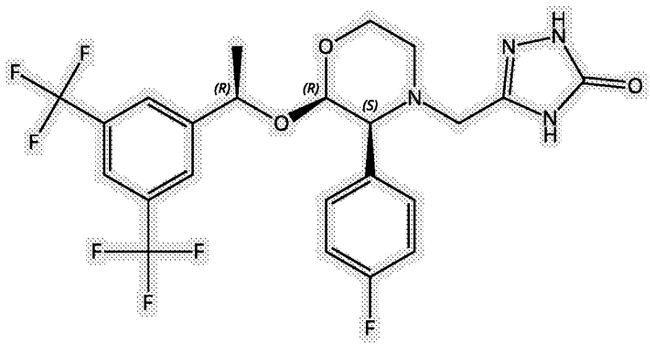
IT 64-17-5, Ethanol, biological studies 77-86-1, Tris buffer 143-19-1, Sodium oleate 7732-18-5, Water, biological studies
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(method of administering emulsion formulations of NK-1 receptor antagonist)

IT 2392-39-4, Dexamethasone sodium phosphate 147116-64-1, Ezlopitant 147116-67-4, Maropitant 170729-80-3, Aprepitant 290296-68-3, Befetupitant 290297-26-6, Netupitant 334476-46-9, Vestipitant 414910-27-3, Casopitant 552292-08-7, Rolapitant 579475-18-6, Orvepitant 860642-69-9, Ser-lopitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(method of administering emulsion formulations of NK-1 receptor antagonist)

IT 170729-80-3, Aprepitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(method of administering emulsion formulations of NK-1 receptor antagonist)

RN 170729-80-3 CAPLUS

CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
AU 2019214872 A1	AU 2019-214872	Register
EP 3746051 A1	EP 2019-705044	Register|Federated Reg.
JP 2021512091 T	JP 2020-541556	Register|Global Dossier
US 20190231688 A1	US 2019-16261459	Register|Global Dossier
WO 2019152430 A1	WO 2019-US15708	Register|Global Dossier

L5 ANSWER 11 OF 18 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2019:425605 CAPLUS Full-text
DOCUMENT NUMBER: 170:406568
TITLE: Aprepitant emulsion for treating nausea and vomiting after chemotherapy in tumor patient, and its preparation method and application
INVENTOR(S): Xu, Wendong; Tang, Shunzhi; Yuan, Cheng; Niu, Yawei; Fu, Yuping; Wang, Guocai; Guan, Weijian; Mou, Xiaonan; He, Jie; Li, Jirong; Yang, Yuqiong; Li, Yao
PATENT ASSIGNEE(S): Guangzhou Baiyunshan Hanfang Pharmaceutical Co., Ltd., Peop. Rep. China
ULTIMATE OWNER: GUANGZHOU BAIYUNSHAN PHARMACEUTICAL HOLDINGS CO., LTD.
ULTIMATE OWNER STANDARD: Guangzhou Baiyunshan Pharma
SOURCE: Faming Zhuanli Shenqing, 14pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 109432002	A	20190308	CN 2018-11587906	20181225

PRIORITY APPLN. INFO.: CN 2018-11587906 20181225
PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
CN 109432002	A	Dead	20220825

OTHER SOURCE(S): CASFORMULTNS 2019:425605
AB An aprepitant emulsion useful for reducing nausea and vomiting in the pre and post-chemotherapy of the tumor, improving immunity and nutritional support of the tumor patient, and reducing acute and delayed nausea and vomiting in high-dose cisplatin combined with high-dose sensitized cancer chemotherapy is provided. The aprepitant emulsion comprises the following components in mass %: 0.05-2.5 of aprepitant, 10-30 of oil phase solvent, 0.8-18 of emulsifier, 0.03-0.6 of stabilizer, 1-5 of isotonicity regulator, and further comprising a pH regulator, balance being purified water, where the pH of the emulsion is 5.5-8. The prepn. method comprises the following steps: (1) weighing the oil phase solvent, emulsifier and antioxidant, heating in a water bath, dissolving all the emulsifiers, and adding aprepitant and dissolving well to obtain an oil phase; (2) weighing stabilizer, isotonicity regulator, pH regulator,

adding to purified water, and heating in water bath to obtain water phase; (3) slowly adding the oil phase to the water phase, shearing at high speed under stirring, adding the remaining purified water with high speed stirring to obtain colostrum; (4) subjecting obtained colostrum to microfluidization to obtain a final emulsion ; and (5) filling the colostrum with nitrogen, sealing and sterilizing in a rotary sterilizing pot to obtain an aprepitant emulsion .

IPCI A61K0009-107; A61K0031-5377; A23L0033-10; A23P0010-00; A61P0001-08; A61P0035-00

IPCR A61K0009-107 [I]; A23L0033-10 [I]; A23P0010-00 [I]; A61K0031-5377 [I]; A61P0001-08 [I]; A61P0035-00 [I]

CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1

ST aprepitant pharmaceutical emulsion antinausea chemotherapy

IT Antiemetics
Antioxidants
Chemotherapy
Emulsifying agents
Health products
Nausea
Pharmaceutical emulsions
Pharmaceutical tonicity modifiers
Stabilizing agents
Vomiting
pH
(aprepitant emulsion for treating nausea and vomiting after chemotherapy in tumor patient, and its prepn. method and application)

IT Egg yolk lecithins
Fatty acids
Phosphatidylcholines
Phosphatidylglycerols
Soya lecithins
Tocopherols
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aprepitant emulsion for treating nausea and vomiting after chemotherapy in tumor patient, and its prepn. method and application)

IT Phosphatidylcholines
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(egg yolk; aprepitant emulsion for treating nausea and vomiting after chemotherapy in tumor patient, and its prepn. method and application)

IT Coix lacryma-jobi ma-yuen
(seed, oil; aprepitant emulsion for treating nausea and vomiting after chemotherapy in tumor patient, and its prepn. method and application)

IT Ganoderma lucidum
(spore oil; aprepitant emulsion for treating nausea and vomiting after chemotherapy in tumor patient, and its prepn. method and application)

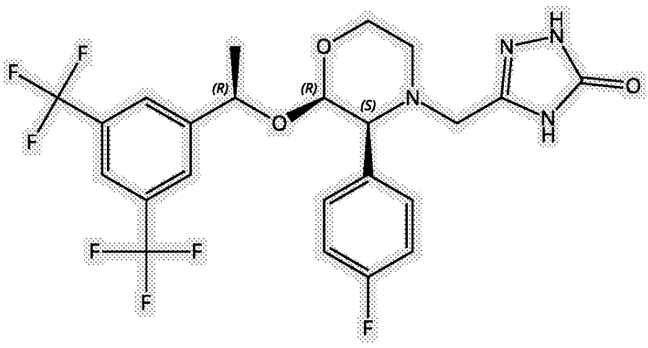
IT 1310-73-2, Sodium hydroxide, uses 7647-01-0, Hydrochloric acid, uses
RL: NUU (Other use, unclassified); USES (Uses)
(aprepitant emulsion for treating nausea and vomiting after chemotherapy in tumor patient, and its prepn. method and application)

IT 50-99-7, D-Glucose, biological studies 56-81-5, Glycerin, biological studies 69-65-8, D-Mannitol 112-80-1, Oleic acid, biological studies 143-19-1, Sodium oleate 7631-90-5, Sodium bisulfite 7647-14-5, Sodium chloride, biological studies 7681-57-4, Sodium metabisulfite 7772-98-7, Sodium thiosulfate 9005-65-6, Polysorbate 80 106392-12-5, Poloxamer 170729-80-3, Aprepitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aprepitant emulsion for treating nausea and vomiting after chemotherapy in tumor patient, and its prepn. method and application)

IT 170729-80-3, Aprepitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aprepitant emulsion for treating nausea and vomiting after chemotherapy in tumor patient, and its prepn. method and application)

RN 170729-80-3 CAPLUS

CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
CN 109432002 A	CN 2018-11587906	Register|Global Dossier

L5 ANSWER 12 OF 18 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2019:340286 CAPLUS Full-text
DOCUMENT NUMBER: 170:348016
TITLE: Aprepitant intravenous emulsion for treating chemotherapy-induced nausea and vomiting, and its preparation method
INVENTOR(S): Yuan, Cheng; Xu, Wendong; Tang, Shunzhi; He, Jie; Niu, Yawei; Fu, Yuping; Wang, Guocai; Guan, Weijian; Mou, Xiaonan; Li, Yao
PATENT ASSIGNEE(S): Guangzhou Baiyunshan Hanfang Pharmaceutical Co., Ltd., Peop. Rep. China
ULTIMATE OWNER: GUANGZHOU BAIYUNSHAN PHARMACEUTICAL HOLDINGS CO., LTD.
ULTIMATE OWNER STANDARD: Guangzhou Baiyunshan Pharma
SOURCE: Faming Zhuanli Shenqing, 11pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 109364023	A	20190222	CN 2018-11588409	20181225

PRIORITY APPLN. INFO.: CN 2018-11588409 20181225
PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
CN 109364023	A	Transitional	20240222

OTHER SOURCE(S): CASFORMULTNS 2019:340286
AB The present invention relates to an i.v. emulsion contg. the following components by mass percentage: 0.05-3% of aprepitant, 5-30% of oil phase solvent, 1.2-18% of emulsifier, 0.03-0.6% of stabilizer, 1-5% of isotonicity adjusting agent, and 0.02-0.5% of antioxidant. The i.v. emulsion further contains a pH adjusting agent and water for injection, where the pH of the i.v. emulsion is 5.5-8.0. The i.v. emulsion has greatly improved the clin. safety, and is utilized for treating acute and delayed nausea and vomiting caused by high-dose cisplatin combined with high-dose sensitizing cancer chemotherapy and reducing nausea and vomiting in the early and middle stages of tumor chemotherapy.
IPCI A61K0009-107; A61K0047-24; A61K0047-12; A61K0031-5377; A61P0035-00; A61P0001-08
IPCR A61K0009-107 [I]; A61K0031-5377 [I]; A61K0047-12 [I]; A61K0047-24 [I]; A61P0001-08 [I]; A61P0035-00 [I]
CC 63-6 (Pharmaceuticals)
ST chemotherapy nausea aprepitant intravenous emulsion
IT Chemotherapy

Homo sapiens
Human
Nausea
Pharmaceutical emulsions
Pharmaceutical intravenous injections
Vomiting
(aprepitant i.v. emulsion for treating chemotherapy-induced nausea and vomiting, and its prepn. method)

IT Castor oil
Egg yolk lecithins
Fish oil
Olive oil
Phosphatidylcholines
Phosphatidylglycerols
Soya phospholipids
Soybean oil
Teaseed oil
Tocopherols
RL: MOA (Modifier or additive use); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aprepitant i.v. emulsion for treating chemotherapy-induced nausea and vomiting, and its prepn. method)

IT Phosphatidylcholines
RL: MOA (Modifier or additive use); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(egg yolk; aprepitant i.v. emulsion for treating chemotherapy-induced nausea and vomiting, and its prepn. method)

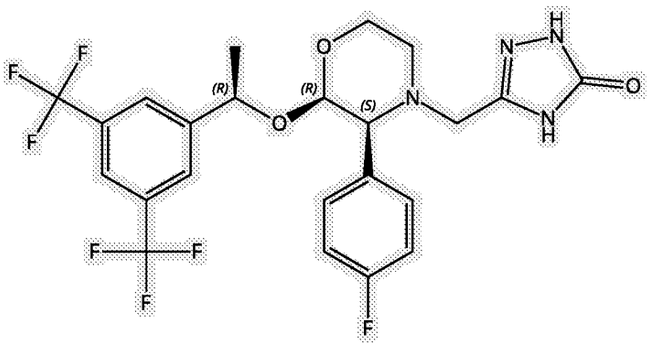
IT 50-99-7, D-Glucose, biological studies 56-81-5, Glycerin, biological studies 69-65-8, D-Mannitol 112-80-1, Oleic acid, biological studies 143-19-1, Sodium oleate 538-23-8, Tricaprylin 538-24-9, Glyceryl trilaurate 621-71-6, Glyceryl tricaprate 1310-73-2, Sodium hydroxide, biological studies 7631-90-5, Sodium hydrogen sulfite 7647-01-0, Hydrochloric acid, biological studies 7647-14-5, Sodium chloride, biological studies 7681-57-4, Sodium metabisulfite 7772-98-7, Sodium thiosulfate 9005-65-6, Polysorbate 80 11140-04-8, Glyceryl caprylate 106392-12-5, Poloxamer
RL: MOA (Modifier or additive use); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aprepitant i.v. emulsion for treating chemotherapy-induced nausea and vomiting, and its prepn. method)

IT 7727-37-9, Nitrogen, uses
RL: NUU (Other use, unclassified); USES (Uses)
(aprepitant i.v. emulsion for treating chemotherapy-induced nausea and vomiting, and its prepn. method)

IT 170729-80-3, Aprepitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aprepitant i.v. emulsion for treating chemotherapy-induced nausea and vomiting, and its prepn. method)

IT 170729-80-3, Aprepitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aprepitant i.v. emulsion for treating chemotherapy-induced nausea and vomiting, and its prepn. method)

RN 170729-80-3 CAPLUS
CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
CN 109364023 A	CN 2018-11588409	Register|Global Dossier

L5 ANSWER 13 OF 18 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2018:2521745 CAPLUS Full-text
DOCUMENT NUMBER: 170:140265
TITLE: High stability aprepitant nano-emulsion and preparation method thereof
INVENTOR(S): Fu, Jifeng; Wang, Wenjuan; Guo, Jia; Zhang, Liancheng
PATENT ASSIGNEE(S): Beijing Ruiyue Biomedical Technology Co., Ltd., Peop. Rep. China
ULTIMATE OWNER: BEIJING RUIYUE BIOLOGY MEDICAL TECH
ULTIMATE OWNER STANDARD: BEIJING RUIYUE BIOLOGY MEDICAL TECH
SOURCE: Faming Zhuanli Shenqing, 9pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

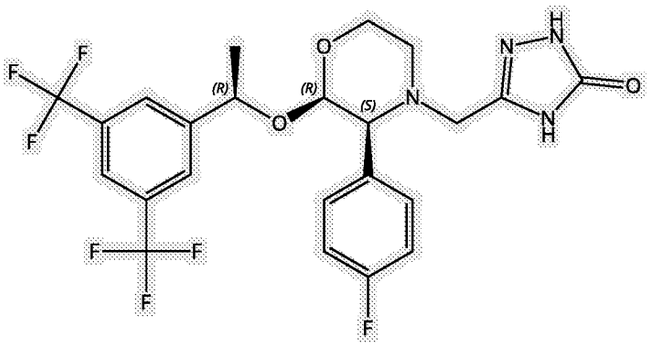
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 109010272	A	20181218	CN 2018-11133738	20180927

PRIORITY APPLN. INFO.: CN 2018-11133738 20180927
PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
CN 109010272	A	Dead	20230323

OTHER SOURCE(S): CASFORMULTNS 2018:2521745
AB The invention discloses a nano-emulsion of aprepitant as shown in structure I and prepn. method thereof. The nano-emulsion is prepd. with the following components in percentage by wt.: aprepitant 0.05-1.5%, soybean oil 2-20%, egg yolk lecithin 5-20%, ethanol 0.5-5%, sodium oleate 0.05-2%, sucrose 2-10%, and water for injection 40-80%. The sodium oleate is added into the oil phase to rapidly stabilize the oil droplets when contacts with the aq. phase, thereby increasing the stability of the nano-emulsion .
IPCI A61K0009-107; A61K0047-12; A61K0047-44; A61K0047-24; A61K0047-10; A61K0047-26; A61K0031-5377; A61P0001-08
IPCR A61K0009-107 [I]; A61K0031-5377 [I]; A61K0047-10 [I]; A61K0047-12 [I]; A61K0047-24 [I]; A61K0047-26 [I]; A61K0047-44 [I]; A61P0001-08 [I]
CC 63-6 (Pharmaceuticals)
IT Pharmaceutical nanoemulsions
(High stability aprepitant nano-emulsion and prepn. method thereof)
IT Egg yolk lecithins
Soybean oil
RL: MOA (Modifier or additive use); NANO (Nanomaterial); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(High stability aprepitant nano-emulsion and prepn. method thereof)
IT 57-50-1, D-Sucrose, biological studies 143-19-1, Sodium oleate
RL: MOA (Modifier or additive use); NANO (Nanomaterial); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(High stability aprepitant nano-emulsion and prepn. method thereof)
IT 170729-80-3, Aprepitant
RL: NANO (Nanomaterial); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(High stability aprepitant nano-emulsion and prepn. method thereof)
IT 170729-80-3, Aprepitant
RL: NANO (Nanomaterial); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(High stability aprepitant nano-emulsion and prepn. method thereof)
RN 170729-80-3 CAPLUS
CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
CN 109010272 A	CN 2018-11133738	Register|Global Dossier

L5 ANSWER 14 OF 18 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2018:2521716 CAPLUS Full-text
DOCUMENT NUMBER: 170:154781
TITLE: Fat emulsion injection of aprepitant with improved stability for treating chemotherapy-induced nausea and vomiting
INVENTOR(S): Liu, Jie; Liu, Yun; Zhou, Lili
PATENT ASSIGNEE(S): Fubicheng (Shanghai) Pharmaceutical Technology Co., Ltd., Peop. Rep. China
ULTIMATE OWNER: FUBICHENG SHANGHAI MEDICINE TECH
ULTIMATE OWNER STANDARD: FUBICHENG SHANGHAI MEDICINE TECH
SOURCE: Faming Zhuanli Shenqing, 11pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 109010269	A	20181218	CN 2018-10979074	20180827
CN 109010269	B	20210420		

PRIORITY APPLN. INFO.: CN 2018-10979074 20180827
PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
CN 109010269	A	Alive	20201121
CN 109010269	B	Alive	20210430

OTHER SOURCE(S): CASFORMULTNS 2018:2521716

AB The title fat emulsion injection of aprepitant for treating chemotherapy-induced nausea and vomiting is prepd. from aprepitant, egg yolk lecithin , oil for injection (coconut oil, soybean oil, or olive oil), glycine, polyvinylpyrrolidone, water for injection, sodium oleate, and C1-5 short-chain alc. (ethanol or propanediol). The inventive prepn. has improved stability and reduced vascular irritation.

IPCI A61K0009-107; A61K0031-5377; A61K0047-18; A61K0047-32; A61K0031-439; A61K0009-08; A61P0001-08

IPCR A61K0009-107 [I]; A61K0009-08 [I]; A61K0031-439 [I]; A61K0031-5377 [I]; A61K0047-18 [I]; A61K0047-32 [I]; A61P0001-08 [I]

CC 63-6 (Pharmaceuticals)

ST aprepitant fat emulsion injection chemotherapy induced nausea vomiting antiemetic

IT Short-chain alcohols
RL: MOA (Modifier or additive use); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(C1-5; fat emulsion injection of aprepitant with improved stability for treating chemotherapy-induced nausea and vomiting)

IT Egg yolk lecithins
RL: MOA (Modifier or additive use); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(Lipoid E 80; fat emulsion injection of aprepitant with improved stability for treating chemotherapy-induced nausea and vomiting)

IT Antiemetics
Homo sapiens
Human
Nausea
Neurokinin 1 receptor antagonists
Pharmaceutical emulsions
Pharmaceutical injections
Vomiting
(fat emulsion injection of aprepitant with improved stability for treating chemotherapy-induced nausea and vomiting)

IT Coconut oil
Olive oil
Safflower oil
Soybean oil
RL: MOA (Modifier or additive use); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(fat emulsion injection of aprepitant with improved stability for treating chemotherapy-induced nausea and vomiting)

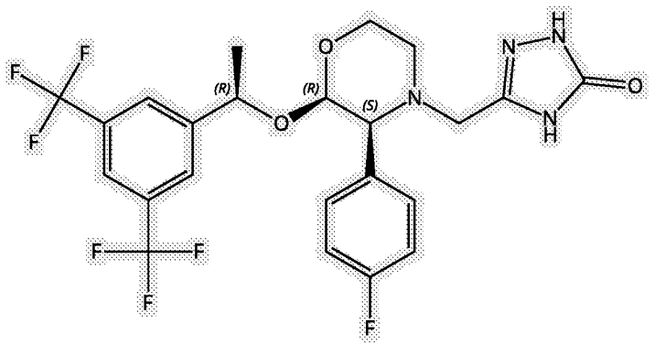
IT 56-40-6, Glycine, biological studies 64-17-5, Ethanol, biological studies 143-19-1, Sodium oleate 9003-39-8, Polyvinylpyrrolidone 26264-14-2, Propanediol
RL: MOA (Modifier or additive use); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(fat emulsion injection of aprepitant with improved stability for treating chemotherapy-induced nausea and vomiting)

IT 170729-80-3, Aprepitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(fat emulsion injection of aprepitant with improved stability for treating chemotherapy-induced nausea and vomiting)

IT 170729-80-3, Aprepitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(fat emulsion injection of aprepitant with improved stability for treating chemotherapy-induced nausea and vomiting)

RN 170729-80-3 CAPLUS

CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

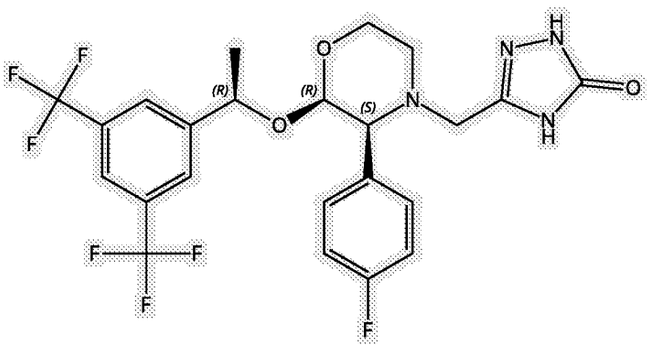
LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
CN 109010269 A	CN 2018-10979074	Register|Global Dossier
CN 109010269 B	CN 2018-10979074	Register|Global Dossier

L5 ANSWER 15 OF 18 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2016:1723954 CAPLUS Full-text
DOCUMENT NUMBER: 172:411315
TITLE: Optimization of the Ussing chamber setup with excised rat intestinal segments for dissolution/permeation experiments of poorly soluble drugs
AUTHOR(S): Forner, Kristin; Roos, Carl; Dahlgren, David; Kesisoglou, Filippos; Konerding, Moritz A.; Mazur, Johanna; Lennernaes, Hans; Langguth, Peter
CORPORATE SOURCE: Department of Pharmaceutical Technology and Biopharmaceutics, Johannes Gutenberg University, Mainz, Germany
SOURCE: Drug Development and Industrial Pharmacy (2017), 43(2), 338-346
CODEN: DDIPD8; ISSN: 0363-9045
DIGITAL OBJECT ID: 10.1080/03639045.2016.1251449
PUBLISHER: Taylor & Francis Ltd.
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English

AB Prediction of the in vivo absorption of poorly sol. drugs may require simultaneous dissoln./permeation expts. In vivo predictive media have been modified for permeation expts. with Caco-2 cells, but not for excised rat intestinal segments. The present study aimed at improving the setup of dissoln./permeation expts. with excised rat intestinal segments by assessing suitable donor and receiver media. The regional compatibility of rat intestine in Ussing chambers with modified Fasted and Fed State Simulated Intestinal Fluids (Fa/FeSSIFmod) as donor media was evaluated via several parameters that reflect the viability of the excised intestinal segments. Receiver media that establish sink conditions were investigated for their foaming potential and toxicity. Dissoln./permeation expts. with the optimized conditions were then tested for two particle sizes of the BCS class II drug aprepitant. Fa/FeSSIFmod were toxic for excised rat ileal sheets but not duodenal sheets, the compatibility with jejunal segments depended on the bile salt concn. A non-foaming receiver medium contg. bovine serum albumin (BSA) and Antifoam B was nontoxic. With these conditions, the permeation of nanosized aprepitant was higher than of the unmilled drug formulations. The compatibility of Fa/FeSSIFmod depends on the excised intestinal region. The chosen conditions enable dissoln./permeation expts. with excised rat duodenal segments. The expts. correctly predicted the superior permeation of nanosized over unmilled aprepitant that is obsd. in vivo. The optimized setup uses FaSSIFmod as donor medium, excised rat duodenal sheets as permeation membrane and a receiver medium contg. BSA and Antifoam B.

CC 63-5 (Pharmaceuticals)
Section cross-reference(s): 9
IT Lecithins
RL: MOA (Modifier or additive use); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(optimization of Ussing chamber setup with excised rat intestinal segments for dissoln./permeation expts. of poorly sol. drugs)
IT 57-88-5, Cholesterol, biological studies 145-42-6, Sodium taurocholate 9002-96-4, Vit E TPGS) 54693-50-4, Antifoam B emulsion
RL: MOA (Modifier or additive use); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(optimization of Ussing chamber setup with excised rat intestinal segments for dissoln./permeation expts. of poorly sol. drugs)
IT 81-81-2, Warfarin 15307-86-5, Diclofenac 29122-68-7, Atenolol 170729-80-3, Aprepitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(optimization of Ussing chamber setup with excised rat intestinal segments for dissoln./permeation expts. of poorly sol. drugs)
IT 170729-80-3, Aprepitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(optimization of Ussing chamber setup with excised rat intestinal segments for dissoln./permeation expts. of poorly sol. drugs)
RN 170729-80-3 CAPLUS
CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

OS.CITING REF COUNT: 11 THERE ARE 11 CAPLUS RECORDS THAT CITE THIS RECORD (11 CITINGS)
REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 16 OF 18 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2016:473657 CAPLUS Full-text
DOCUMENT NUMBER: 164:387016
TITLE: Emulsion formulations of aprepitant
INVENTOR(S): Ottoboni, Thomas B.; Han, Han
PATENT ASSIGNEE(S): Heron Therapeutics, Inc., USA
ULTIMATE OWNER: HERON THERAPEUTICS, INC.
ULTIMATE OWNER STANDARD: HERON THERAPEUTICS, INC.
SOURCE: PCT Int. Appl., 36pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2016044784	A1	20160324	WO 2015-US51050	20150918
US 20160082013	A1	20160324	US 2015-14859013	20150918
US 9808465	B2	20171107		

KR 2017056575	A	20170523	KR 2017-7008598	20150918
KR 2424837	B1	20220725		
CN 106852118	A	20170613	CN 2015-80050449	20150918
EP 3193830	A1	20170726	EP 2015-772163	20150918
EP 3193830	B1	20231101		
EP 3193830	C0	20231101		
JP 2017533183	T	20171109	JP 2017-514863	20150918
JP 6741655	B2	20200819		
US 20160206622	A1	20160721	US 2016-15083071	20160328
US 9561229	B2	20170207		
US 20170112847	A1	20170427	US 2017-15398928	20170105
US 10500208	B2	20191210		
US 20180000828	A1	20180104	US 2017-15705201	20170914
US 9974793	B2	20180522		
US 20180000829	A1	20180104	US 2017-15705208	20170914
US 9974794	B2	20180522		
JP 2019196398	A	20191114	JP 2019-137539	20190726
US 20200197404	A1	20200625	US 2019-16669262	20191030
US 10953018	B2	20210323		
US 20210186981	A1	20210624	US 2021-17194114	20210305
JP 2022092040	A	20220621	JP 2022-66236	20220413

PRIORITY APPLN. INFO.:

US 2014-62052948	P	20140919
JP 2017-514863	A3	20150918
US 2015-14859013	A1	20150918
WO 2015-US51050	W	20150918
US 2016-15083071	A1	20160328
US 2017-15398928	A1	20170105
JP 2019-137539	A3	20190726
US 2019-16669262	A1	20191030

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
WO 2016044784	A1	Dead	20201202
US 20160082013	A1	Alive	20201121
US 9808465	B2	Alive	20201120
KR 2017056575	A	Alive	20220602
KR 2424837	B1	Alive	20220811
CN 106852118	A	Transitional	20240307
EP 3193830	A1	Alive	20201201
EP 3193830	C0	Alive	20240104
JP 2017533183	T	Alive	20201121
JP 6741655	B2	Alive	20201121
US 20160206622	A1	Alive	20201120
US 9561229	B2	Alive	20201120
US 20170112847	A1	Alive	20201120
US 10500208	B2	Alive	20201120
US 20180000828	A1	Alive	20201121
US 9974793	B2	Alive	20201120
US 20180000829	A1	Alive	20201121
US 9974794	B2	Alive	20201120
JP 2019196398	A	Dead	20231026
US 20200197404	A1	Alive	20201121
US 10953018	B2	Alive	20210401
US 20210186981	A1	Alive	20231012
JP 2022092040	A	Dead	20231207

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OTHER SOURCE(S): CASFORMULTNS 2016:473657

AB Disclosed herein are novel pharmaceutical formulations of aprepitant suitable for parenteral administration including i.v. administration. Also included are formulations including both aprepitant and dexamethasone sodium phosphate. The pharmaceutical formulations are stable oil-in-water emulsions for non-oral treatment of emesis and are particularly useful for treatment of subjects undergoing cancer chemotherapy.

IPCI A61K0009-00 [I]; A61K0047-10 [I]; A61K0047-44 [I]; A61K0047-24 [I]; A61K0047-12 [I]; A61K0047-26 [I]

IPCR A61K0009-00 [I]; A61K0047-10 [I]; A61K0047-12 [I]; A61K0047-24 [I]; A61K0047-26 [I]; A61K0047-44 [I]

CC 63-6 (Pharmaceuticals)

ST emulsion formulation aprepitant

IT Buffers
Emulsifying agents
Parenteral drug delivery systems

Particle size distribution
Pharmaceutical emulsions
Pharmaceutical intravenous injections
Pharmacokinetics
Stability
Zeta potential
pH
(emulsion formulations of aprepitant)

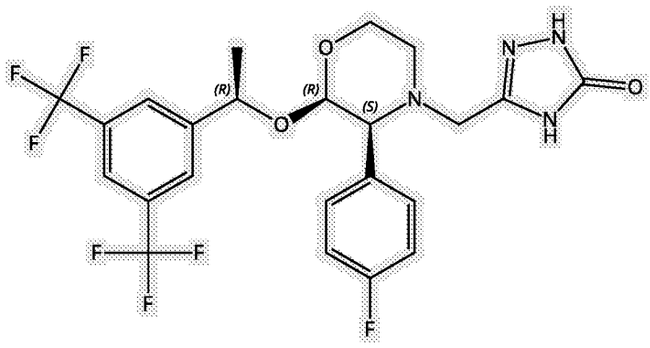
IT Alcohols
Egg yolk lecithins
Phospholipids
Soybean oil
RL: COS (Cosmetic use); BIOL (Biological study); USES (Uses)
(emulsion formulations of aprepitant)

IT 2392-39-4 170729-80-3
RL: PKT (Pharmacokinetics); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(emulsion formulations of aprepitant)

IT 64-17-5, Ethanol, biological studies 77-86-1 143-19-1
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(emulsion formulations of aprepitant)

IT 170729-80-3
RL: PKT (Pharmacokinetics); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(emulsion formulations of aprepitant)

RN 170729-80-3 CAPLUS
CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
CN 106852118 A	CN 2015-80050449	Register|Global Dossier
EP 3193830 A1	EP 2015-772163	Register|Federated Reg.
EP 3193830 B1	EP 2015-772163	Register|Federated Reg.
EP 3193830 C0	EP 2015-772163	Register|Federated Reg.
JP 2017533183 T	JP 2017-514863	Register|Global Dossier
JP 6741655 B2	JP 2017-514863	Register|Global Dossier
JP 2019196398 A	JP 2019-137539	Register|Global Dossier
JP 2022092040 A	JP 2022-66236	Register|Global Dossier
KR 2017056575 A	KR 2017-7008598	Register|Global Dossier
KR 2424837 B1	KR 2017-7008598	Register|Global Dossier
US 20160082013 A1	US 2015-14859013	Register|Global Dossier
US 9808465 B2	US 2015-14859013	Register|Global Dossier
US 20160206622 A1	US 2016-15083071	Register|Global Dossier

US 9561229 B2	US 2016-15083071	Register|Global Dossier
US 10500208 B2	US 2017-15398928	Register|Global Dossier
US 20170112847 A1	US 2017-15398928	Register|Global Dossier
US 20180000828 A1	US 2017-15705201	Register|Global Dossier
US 9974793 B2	US 2017-15705201	Register|Global Dossier
US 20180000829 A1	US 2017-15705208	Register|Global Dossier
US 9974794 B2	US 2017-15705208	Register|Global Dossier
US 10953018 B2	US 2019-16669262	Register|Global Dossier
US 20200197404 A1	US 2019-16669262	Register|Global Dossier
US 20210186981 A1	US 2021-17194114	Register|Global Dossier
WO 2016044784 A1	WO 2015-US51050	Register|Global Dossier

L5 ANSWER 17 OF 18 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2015:1390403 CAPLUS Full-text
DOCUMENT NUMBER: 163:369597
TITLE: Compositions of pentosan polysulfate salts for oral administration and methods of use
INVENTOR(S): Parsons, C. Lowell; Goldberg, Michael; Meenan, Christopher P.
PATENT ASSIGNEE(S): Urigen Pharmaceuticals, Inc., USA
ULTIMATE OWNER: PLATINUM MONTAUR LIFE SCIENCES
ULTIMATE OWNER STANDARD: PLATINUM MONTAUR LIFE SCIENCES
SOURCE: PCT Int. Appl., 248pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2015127416	A1	20150827	WO 2015-US17205		20150224
CA 2949480	A1	20150827	CA 2015-2949480		20150224
AU 2015218642	A1	20161006	AU 2015-218642		20150224
EP 3110427	A1	20170104	EP 2015-751441		20150224
KR 2017003527	A	20170109	KR 2016-7026610		20150224
CN 106456662	A	20170222	CN 2015-80022057		20150224
JP 2017512757	T	20170525	JP 2016-554267		20150224
US 20170189443	A1	20170706	US 2016-15121312		20160824
PRIORITY APPLN. INFO.:			US 2014-61943824	P	20140224
			WO 2015-US17205	W	20150224

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
WO 2015127416	A1	Dead	20201201
CA 2949480	A1	Dead	20220428
AU 2015218642	A1	Dead	20210318
EP 3110427	A1	Dead	20210729
KR 2017003527	A	Alive	20201121
CN 106456662	A	Dead	20201121
JP 2017512757	T	Alive	20201120
US 20170189443	A1	Dead	20210324

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): MARPAT 163:369597; CASFORMULTNS 2015:1390403
AB The invention is directed to a pharmaceutical compn. comprising: (1) a therapeutically effective quantity of sodium pentosan polysulfate; (2) a quantity of a penetration enhancer sufficient to improve the bioavailability of the sodium pentosan polysulfate; and (3) optionally, a pharmaceutically acceptable carrier and to methods for the oral administration of sodium pentosan polysulfate with improved bioavailability for the treatment of interstitial cystitis and other urinary tract diseases and conditions. Such compns. and methods allow the administration of sodium pentosan polysulfate at lower dosages to reduce the frequency and severity of side effects.
IPCI A61K0031-715 [I]; C07H0005-10 [I]; A61K0047-14 [I]; A61P0019-02 [I]
IPCR A61K0031-715 [I]; A61K0047-14 [I]; A61P0019-02 [I]; C07H0005-10 [I]
CC 1-12 (Pharmacology)
IT Agglomeration preventers
Alzheimer disease
Analgesics
Ankylosing spondylitis
Anti-Alzheimer agents
Anti-HIV agents

Anti-inflammatory agents
Antiarthritics
Antiasthmatics
Antiatherosclerotics
Antifoaming agents
Antioxidants
Antipsoriatic agents
Antirheumatic agents
Antitumor agents
Asthma
Atherosclerosis
Bioavailability
Blood coagulation disorders
Bos taurus
Buccal drug delivery systems
Buffers
Canis familiaris
Capra hircus
Cat
Cattle
Chelating agents
Cholinergic antagonists
Coating materials
Coloring materials
Combination chemotherapy
Complexing agents
Cosmetic fragrance products
Creutzfeldt-Jakob disease
Cystitis
Dog
Drug bioavailability
Drug toxicity
Drying agents
Emulsifying agents
Equus caballus
Escherichia coli
Felis catus
Filter aids
Flavor
Goat
HIV infection
Homo sapiens
Horse
Human
Humectants
Inflammation
Intervertebral disc degeneration
Ionic surfactants
Juvenile rheumatoid arthritis
Lower urinary tract disease
Lupus erythematosus
Matrix metalloproteinase inhibitors
Micelles
Mule
Multiple sclerosis
Myocarditis
NMDA receptor antagonists
Nanoparticles
Narcotics
Nonionic detergents
Nonionic surfactants
Nonsteroidal anti-inflammatory agents
Oral drug delivery systems
Osteoarthritis
Osteonecrosis
Overactive bladder
Ovis aries
Pain
Peptidomimetics
Permeation enhancers
Pharmaceutical binders
Pharmaceutical carriers

Pharmaceutical diluents
Pharmaceutical disintegrants
Pharmaceutical emulsions
Pharmaceutical fillers
Pharmaceutical films
Pharmaceutical glidants
Pharmaceutical oils
Pharmaceutical viscosity enhancers
Plasticizers
Preservatives
Prion diseases
Prostate gland neoplasm
Prostatitis
Psoriasis
Psoriatic arthritis
Renal calculi
Rheumatoid arthritis
Selective estrogen receptor modulators
Sheep
Solubilizers
Solvents
Sorbents
Stiffening materials
Sublingual drug delivery systems
Sus scrofa domestica
Sweetening agents
Swine
Tachykinin antagonists
Tranquilizers
Urinary system infection
Wetting agents
(compns. of pentosan polysulfate salts for oral administration and methods of use)

IT Acrylic polymers
Acylcarnitines
Amino acids
Bile salts
Bone morphogenetic protein 7
Bone sialoproteins
Cartilage oligomeric matrix protein
Collagen type I
Collagen type II
Collagen type IX
Collagen type XI
Collagens
Crown compounds
Dendrimers
Diglycerides
Estrogens
Fatty acids
Insulin-like growth factor-binding protein 3
Lecithins
Matrix proteins
Medium-chain fatty acids
Monoclonal antibodies
Monoglycerides
Opioids
Osteocalcins
Osteonectin
Osteopontin
Peptides
Polyanhydrides
Polyoxyalkylenes
Proteins
Salicylates
Steroidal hormones
Sulfonanilides
Terpenes
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. of pentosan polysulfate salts for oral administration and methods of use)

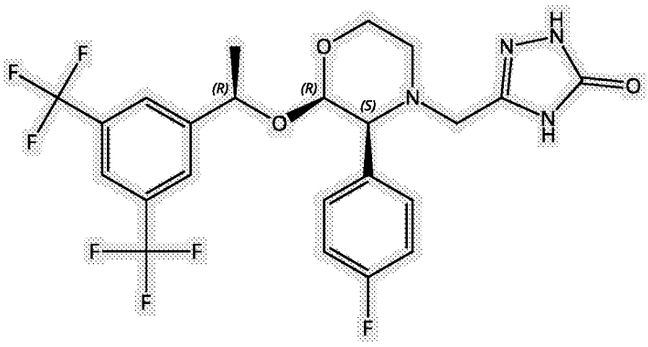
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170277-31-3, Infliximab 170566-84-4, Lanepitant 170713-75-4
170729-80-3, Aprepitant 172673-20-0, Fosaprepitant
173937-91-2, Atrasentan 175033-36-0, NCX4016 177036-94-1, Ambrisentan
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180384-57-0, Tezosentan
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)
(compns. of pentosan polysulfate salts for oral administration and
methods of use)

IT 170729-80-3, Aprepitant
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)
(compns. of pentosan polysulfate salts for oral administration and
methods of use)

RN 170729-80-3 CAPLUS

CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phen
yl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX
NAME)



Absolute stereochemistry shown
Rotation (+)

OS.CITING REF COUNT: 4 THERE ARE 4 CAPLUS RECORDS THAT CITE THIS RECORD (4 CITINGS)
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
AU 2015218642 A1	AU 2015-218642	Register
CA 2949480 A1	CA 2015-2949480	Register
CN 106456662 A	CN 2015-80022057	Register|Global Dossier
EP 3110427 A1	EP 2015-751441	Register|Federated Reg.
JP 2017512757 T	JP 2016-554267	Register|Global Dossier
KR 2017003527 A	KR 2016-7026610	Register|Global Dossier
US 20170189443 A1	US 2016-15121312	Register|Global Dossier
WO 2015127416 A1	WO 2015-US17205	Register|Global Dossier

L5 ANSWER 18 OF 18 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2013:496643 CAPLUS Full-text
DOCUMENT NUMBER: 159:140262
TITLE: Preparation of aprepitant emulsion for intravenous injection
AUTHOR(S): Zhou, Wei; Chen, Fei; Chen, Ning; Mao, Ke
CORPORATE SOURCE: School of Pharmaceutical, Jiangsu Provincial Institute of Materia Medica, Nanjing University of Technology, Nanjing, Jiangsu Province, 211816, Peop. Rep. China

SOURCE: Zhongguo Yiyao Gongye Zazhi (2012), 43(12), 1003-1006
CODEN: ZYGZEA; ISSN: 1001-8255
PUBLISHER: Zhongguo Yiyao Gongye Zazhi Bianjibu
DOCUMENT TYPE: Journal
LANGUAGE: Chinese

AB The formulation of aprepitant emulsion for i.v. injection was optimized by single factor test and orthogonal design. The properties, such as appearance, particle size, ζ potential and stability of the product were investigated. The results showed that the type and amt. of emulsifier as well as the amt. of oleic acid had the greater effect on stability. The optimal formulation of aprepitant emulsion was as follows: aprepitant was 0.25%, soybean oil was 15%, egg yolk lecithin ESO was 2.5% and oleic acid was 0.125%. The appearance of the product was ivory. The av. particle size, PDI, centrifugal stability const. (Ke), ζ potential, pH value and drug content of the product before and after sterilization were (215.71±1.26) and (220.3±0.53) nm, 0.203±0.016 and 0.210±0.009, 0.21±0.01 and 0.34±0.01, (-37.5±0.2) and (-37.6±0.5) mV, 7.21±0.23 and 7.31±0.30, (101.03±0.89)% and (101.12±1.20)%, resp.

CC 63-6 (Pharmaceuticals)

ST aprepitant emulsion intravenous injection

IT Electric potential
Particle size
Pharmaceutical injections
Sterilization and Disinfection
(prepn. of aprepitant emulsion for i.v. injection)

IT Egg yolk lecithins
Soybean oil
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(prepn. of aprepitant emulsion for i.v. injection)

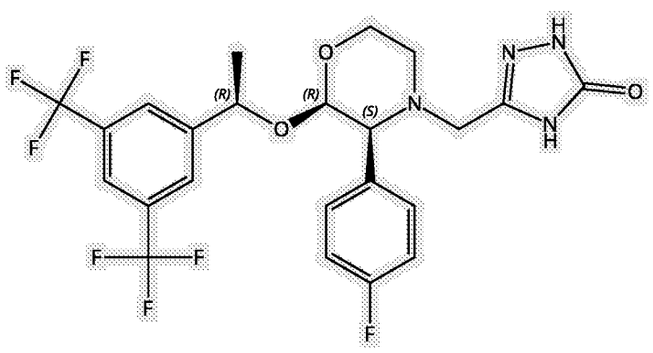
IT 112-80-1, Oleic acid, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(prepn. of aprepitant emulsion for i.v. injection)

IT 170729-80-3, Aprepitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. of aprepitant emulsion for i.v. injection)

IT 170729-80-3, Aprepitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. of aprepitant emulsion for i.v. injection)

RN 170729-80-3 CAPLUS

CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

=> D L4 1-48 IBIB ABS HITIND HITSTR

L4 ANSWER 1 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN

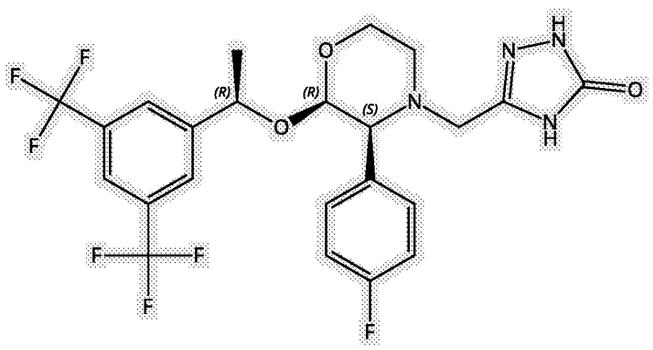
ACCESSION NUMBER: 2024:141628 CAPLUS Full-text
TITLE: Aprepitant emulsion drug composition and preparation method thereof
INVENTOR(S): Chen, Xiangmei; Yu, Changhui; Wang, Xinlong; Lin, Liyang; Shen, Li; Zhao, Dong
PATENT ASSIGNEE(S): Sichuan Kelun Pharmaceutical Research Institute Co., Ltd., Peop. Rep. China
SOURCE: Faming Zhuanli Shenqing, 8pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 117414334	A	20240119	CN 2022-10811953	20220711

PRIORITY APPLN. INFO.: CN 2022-10811953 20220711
PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
CN 117414334	A	Alive	20240125

AB The present invention provides an aprepitant emulsion drug compn. and prepn. method thereof, which has the advantages of high quality and good stability. The method comprises the following steps: stirring and dissolving aprepitant, phospholipid, ethanol and soybean oil to obtain an oil phase, adding an isotonic regulator, the phospholipid and a pH regulator into water for injection, stirring uniformly to obtain a water phase, online shearing and mixing the oil phase and the water phase to prep. a primary emulsion, homogenizing by high-pressure microjet, sterilizing, filtering and filling.
IPCI A61K0009-107; A61K0031-5377; A61K0047-24; A61K0047-44; A61P0001-08
IPCR A61K0009-107 [I]; A61K0031-5377 [I]; A61K0047-24 [I]; A61K0047-44 [I]; A61P0001-08 [I]
CC 63 (Pharmaceuticals)
IT INDEXING IN PROGRESS
IT Egg yolk lecithins
Soybean oil
RL: MOA (Modifier or additive use); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(aprepitant emulsion drug compn. and prepn. method thereof)
IT 170729-80-3, Aprepitant
RL: PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(aprepitant emulsion drug compn. and prepn. method thereof)
IT 170729-80-3, Aprepitant
RL: PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(aprepitant emulsion drug compn. and prepn. method thereof)
RN 170729-80-3 CAPLUS
CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

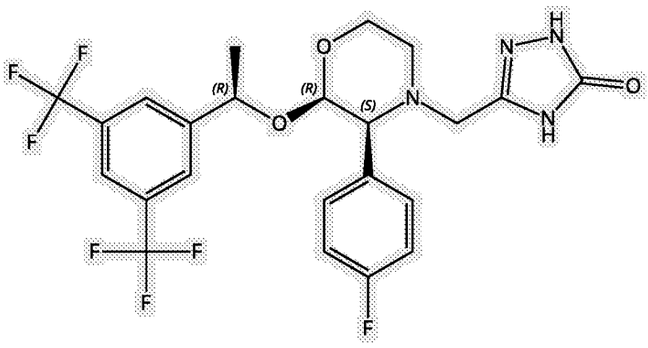
LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
CN 117414334 A	CN 2022-10811953	Register|Global Dossier

L4 ANSWER 2 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2023:1752935 CAPLUS Full-text
DOCUMENT NUMBER: 184:181224
TITLE: Formulation and evaluation of lipid nanoparticulate drug delivery system of Aprepitant for the treatment of Cinv
AUTHOR(S): R., Joan Vijetha; Balamurugan, K.
CORPORATE SOURCE: College of Pharmacy, Sathyabama Institute of Science and Technology, Semmancheri, Chennai, 600119, India
SOURCE: Journal of Pharmaceutical Negative Results (2022), 13(Spec.Iss.10), 5114-5127
CODEN: JPNRBH; ISSN: 2229-7723
URL: https://www.pnrjournal.com/index.php/home/index
DIGITAL OBJECT ID: 10.47750/pnr.2022.13.s10.627
PUBLISHER: ResearchTrentz
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English

AB The present study was to formulate and evaluate the Aprepitant USP is a substance P/neurokinin 1 (NK1) receptor antagonist as nanoparticulate lipid carriers (AP-NLC) drug delivery systems and comparing with the marketed product. The formulations of AP-NLC were prepd. by the homogenization followed by ultrasonication method using the solid lipid as Glyceryl behenate, the liq. lipid Caprylocaproyl polyoxyglycerides and polysorbate 80 as hydrophilic surfactant. Based on the trial expts., the compn. of optimized formulation was AP-NLC blend consist of 125 mg of Aprepitant, 210 mg Glyceryl behenate, 90 mg Caprylocaproyl polyoxyglycerides, 36 mg polysorbate 80 and 20 mg soya lecithin. By liquisolid technique mesoporous silica gel taken was 160.4 mg was mixed with above AP-NLC blend to form from the optimized AP-NLC12 capsules. The AP NLC12 was found to be with mean particle size of mean av. of 200.6 nm with max. intensity of 541.0 nm particles, The dissoln. data demonstrates that the drug release was increased by 5-12% increase in drug release in initial time points upto 3 h as compared to the marketed product and the release is sustained up to 30 h as compared to the 10 h for the marketed product. The drug release kinetics of AP NLC 12 was by Korsmeyer-Peppas model confirms the drug release from a polymeric system and release mechanisms was diffusion followed by erosion.This research is an attempt was made to design Aprepitant USP nanoparticulate lipid carrier drug delivery systems for sustained drug release in treatment chemotherapy induced nausea and vomiting (CINV).

CC 63-6 (Pharmaceuticals)
IT Soya lecithins
RL: NANO (Nanomaterial); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(formulation and evaluation of lipid nanoparticulate drug delivery system of aprepitant for treatment of chemotherapy induced nausea and vomiting)
IT 9005-65-6 18641-57-1 170729-80-3
RL: NANO (Nanomaterial); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(formulation and evaluation of lipid nanoparticulate drug delivery system of aprepitant for treatment of chemotherapy induced nausea and vomiting)
IT 170729-80-3
RL: NANO (Nanomaterial); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(formulation and evaluation of lipid nanoparticulate drug delivery system of aprepitant for treatment of chemotherapy induced nausea and vomiting)
RN 170729-80-3 CAPLUS
CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2023:1213332 CAPLUS Full-text
DOCUMENT NUMBER: 183:142125
TITLE: Personalized starvation therapy for cancer by administering an inhibitor of the mevalonate pathway with a diet low in cholesterol or lipids
INVENTOR(S): Maddocks, Oliver D. K.; Mishra, Swati
PATENT ASSIGNEE(S): Faeth Therapeutics, Inc., USA
ULTIMATE OWNER: FAETH THERAPEUTICS
ULTIMATE OWNER STANDARD: FAETH THERAPEUTICS
SOURCE: PCT Int. Appl., 210pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2023108146	A1	20230615	WO 2022-US81307		20221209
PRIORITY APPLN. INFO.:			US 2021-63288062	P	20211210

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
WO 2023108146	A1	Alive	20230629

AB Disclosed herein are methods of administering an inhibitor of the mevalonate pathway with a diet low in cholesterol or lipids. The methods of the present invention can be used to treat conditions such as cancer.
IPCI A61K0031-33 [I]; A61K0031-045 [I]; A61K0031-395 [I]; A61K0031-01 [N]
IPCR A61K0031-33 [I]; A61K0031-01 [N]; A61K0031-045 [I]; A61K0031-395 [I]
CC 1-6 (Pharmacology)
Section cross-reference(s): 18, 63
IT Castor oil
Lanolin
Lecithins
Tannins
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(personalized starvation therapy for cancer by administering an inhibitor of mevalonate pathway with a diet low in cholesterol or lipids and combination with other agents)
IT 9031-14-5, Lecithin-cholesterol acyltransferase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; personalized starvation therapy for cancer by administering an inhibitor of mevalonate pathway with a diet low in cholesterol or lipids and combination with other agents)
IT 118292-40-3, Tazarotene 119169-78-7, Epristeride 119302-91-9, Rocuronium (Bromide) 119413-54-6, Topotecan (Hydrochloride) 119478-55-6, Danofloxacin (mesylate) 119478-56-7, Meropenem (trihydrate)

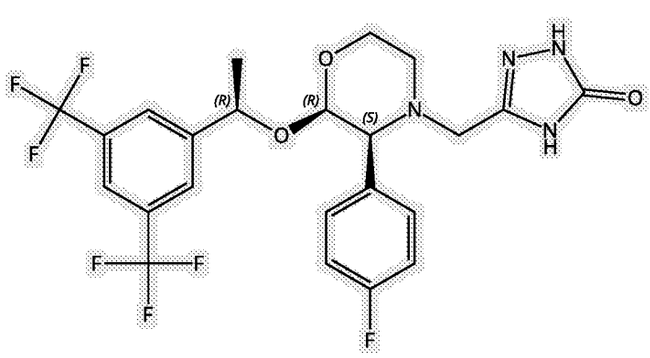
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120876-23-5 121032-29-9, Nelarabine 121123-17-9, Cefprozil
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Iguratimod 124750-99-8, Losartan (potassium) 124832-27-5, Valacyclovir
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Umifenovir (hydrochloride) 132112-35-7, Ropivacaine (hydrochloride
monohydrate) 132203-70-4, Cilnidipine 132539-06-1, Olanzapine
132810-10-7, Blonanserin 132866-11-6, Lercanidipine (hydrochloride)
132907-72-3, Ramosetron (Hydrochloride) 133033-93-9, (±)-Darifenacin
133099-07-7, Darifenacin (hydrobromide) 133454-47-4, Iloperidone
133865-89-1 134308-13-7, Tolcapone 134418-28-3, Dehydroandrographolide
134523-00-5, Atorvastatin 134523-03-8, Atorvastatin calcium
134678-17-4, Lamivudine 135062-02-1, Repaglinide 135159-51-2,
Sarpogrelate (hydrochloride) 135326-22-6, Gadoxetate (Disodium)
135729-62-3, Palonosetron (Hydrochloride) 136087-85-9, Fidarestat
136310-93-5, Tiotropium (Bromide) 136434-34-9, Duloxetine
(hydrochloride) 136470-78-5, Abacavir 136572-09-3, Irinotecan
(hydrochloride trihydrate) 137071-32-0, Pimecrolimus 137234-62-9,
Voriconazole 137281-23-3, Pemetrexed 137862-53-4, Valsartan
137975-06-5, Mozavaptan 138112-76-2, Agomelatine 138402-11-6,
Irbesartan 138470-70-9, Mozavaptan (hydrochloride) 138530-94-6,
(R)-Lansoprazole 138614-30-9, Icatibant (acetate) 138786-67-1,
Pantoprazole (sodium) 138890-62-7, Brinzolamide 138926-19-9,
Ibandronate (Sodium Monohydrate) 138982-67-9, Ziprasidone (hydrochloride
monohydrate) 139110-80-8, Zanamivir 139481-59-7, Candesartan
139755-83-2, Sildenafil 139755-85-4, Lodenafil 140462-76-6,
Olopatadine (hydrochloride) 140678-14-4, Mangafodipir (trisodium)
140898-91-5, Hexaminolevulinate (hydrochloride) 141396-28-3, Argatroban
(monohydrate) 141433-60-5, Berberine (chloride hydrate) 141505-33-1,
Levosimendan 141625-93-6, Dronedarone (Hydrochloride) 141626-36-0,
Dronedarone 141702-36-5, Faropenem daloxate 142128-59-4,
(+)-Ketoconazole 142340-99-6, Adefovir dipivoxil 143388-64-1,
Naratriptan (hydrochloride) 143491-57-0, Emtricitabine 144060-53-7,
Febuxostat 144143-96-4, Eprosartan (mesylate) 144481-98-1, Landiolol
(hydrochloride) 144598-75-4, Paliperidone 144675-97-8, Pixantrone
(dimaleate) 144689-24-7, Olmesartan 144689-63-4, Olmesartan medoxomil
144701-48-4, Telmisartan 145040-37-5, Candesartan Cilexetil
145108-58-3, Dexmedetomidine (hydrochloride) 145202-66-0, Rizatriptan
(benzoate) 145435-72-9, Gamithromycin 145525-41-3, Mitiglinide
(Calcium) 145672-81-7, Cetrorelix (Acetate) 145781-92-6, Goserelin
(acetate) 145821-59-6, Tiagabine (hydrochloride) 146464-95-1,
Pralatrexate 146939-27-7, Ziprasidone 147059-72-1, Trovafloxacin
147084-10-4, Alcaftadine 147098-20-2, Rosuvastatin calcium
147127-20-6, Tenofovir 147221-93-0, Delavirdine (mesylate)
147403-03-0, Azilsartan 147511-69-1, Pitavastatin 147526-32-7,
Pitavastatin calcium 147536-97-8, Bosentan 148408-66-6, Docetaxel
(Trihydrate) 148849-67-6, Ivabradine (hydrochloride) 149003-01-0,
Dexrazoxane (hydrochloride) 149647-78-9, Vorinostat 149709-62-6,
Sacubitril 149845-06-7, Saquinavir (Mesylate) 150322-43-3, Prasugrel
150399-23-8, Pemetrexed (disodium) 150566-71-5, Levamlodipine besylate

150683-30-0, Tolvaptan 150821-03-7, Pranlukast (hemihydrate)
150915-40-5, Tirofiban (hydrochloride monohydrate) 150915-41-6,
Perospirone 151767-02-1, Montelukast (sodium) 152459-95-5, Imatinib
152520-56-4, Nebivolol (hydrochloride) 152658-17-8, Nalfurafine
(hydrochloride) 153439-40-8, Fexofenadine (hydrochloride) 153504-70-2,
Cevimeline (hydrochloride hemihydrate) 153559-49-0, Bexarotene
154229-18-2, Abiraterone acetate 154229-19-3, Abiraterone 154361-50-9,
Capecitabine 154598-52-4, Efavirenz 155141-29-0, Rosiglitazone
(maleate) 155148-31-5, Plerixafor (octahydrochloride) 155206-00-1,
Bimatoprost 155213-67-5, Ritonavir 155270-99-8, Istradefylline
155558-32-0, Hydroxyfasudil (hydrochloride) 155569-91-8, Emamectin
(Benzoate) 156137-99-4, Rapacuronium bromide 157212-55-0, Bosentan
(hydrate) 157283-68-6, Travoprost 157810-81-6, Indinavir (sulfate)
158681-13-1, Rimonabant (Hydrochloride) 158930-17-7, Frovatriptan
succinate hydrate 159351-69-6, Everolimus 159989-64-7, Nelfinavir
159989-65-8, Nelfinavir (Mesylate) 160970-54-7, Silodosin 161715-24-8,
Tebipenem pivoxil 161735-79-1, Rasagiline (mesylate) 161804-20-2
161814-49-9, Amprenavir 161973-10-0, Esomeprazole magnesium
162011-90-7, Rofecoxib 162359-55-9, Fingolimod 162359-56-0, Fingolimod
(hydrochloride) 162401-32-3, Roflumilast 162635-04-3, Temsirolimus
163222-33-1, Ezetimibe 163252-36-6, Clevudine 163253-37-0
163451-81-8, Teriflunomide 163521-08-2, Vilazodone (Hydrochloride)
163521-12-8, Vilazodone 163521-19-5 163680-77-1, Pazufloxacin
(mesylate) 163706-36-3, Cangrelor (tetrasodium) 164650-44-6,
Efinaconazole 164656-23-9, Dutasteride 165800-03-3, Linezolid
165800-06-6, Zoledronic acid (monohydrate) 166663-25-8, Anidulafungin
166734-83-4 167221-71-8, Clevidipine 167933-07-5, Flibanserin
168626-94-6, Conivaptan (hydrochloride) 169590-41-4, Deracoxib
169590-42-5, Celecoxib 170098-38-1, Alvimopan (dihydrate) 170105-16-5,
Imidafenacin 170729-80-3, Aprepitant 171228-49-2,
Posaconazole 171596-29-5, Tadalafil 171599-83-0, Sildenafil (citrate)
172152-36-2, Ilaprazole 172152-50-0, Ilaprazole (sodium) 173334-57-1,
Aliskiren 173334-58-2, Aliskiren (hemifumarate) 173352-39-1
174484-41-4, Tipranavir 174671-46-6, Tavaborole 175865-59-5,
Valganciclovir (hydrochloride) 177036-94-1, Ambrisentan 177834-92-3,
Eletriptan (hydrobromide) 178307-42-1, Revaprazan (hydrochloride)
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)
(personalized starvation therapy for cancer by administering an
inhibitor of mevalonate pathway with a diet low in cholesterol or
lipids and combination with other agents)

IT 170729-80-3, Aprepitant
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)
(personalized starvation therapy for cancer by administering an
inhibitor of mevalonate pathway with a diet low in cholesterol or
lipids and combination with other agents)

RN 170729-80-3 CAPLUS

CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phen
yl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX
NAME)



Absolute stereochemistry shown
Rotation (+)

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
WO 2023108146 A1	WO 2022-US81307	Register|Global Dossier

L4 ANSWER 4 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2022:2496852 CAPLUS Full-text
DOCUMENT NUMBER: 180:210930
TITLE: Compositions having improved bioavailability of therapeutics
INVENTOR(S): Brew, John; Gooding, Daniel; Bannister, Robin M.
PATENT ASSIGNEE(S): TRx Biosciences Limited, UK
ULTIMATE OWNER: TRX BIOSCIENCES
ULTIMATE OWNER STANDARD: TRX BIOSCIENCES
SOURCE: U.S. Pat. Appl. Publ., 202pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20220305125	A1	20220929	US 2022-17656702	20220328
CA 3212583	A1	20221006	CA 2022-3212583	20220328
WO 2022207580	A2	20221006	WO 2022-EP58180	20220328
WO 2022207580	A3	20221229		
AU 2022248850	A1	20231109	AU 2022-248850	20220328
EP 4312978	A2	20240207	EP 2022-718916	20220328
KR 2024021751	A	20240219	KR 2023-7037012	20220328
WO 2023174948	A2	20230921	WO 2023-EP56506	20230314
WO 2023174948	A3	20231026		
US 20240075147	A1	20240307	US 2023-18487486	20231016
IN 202347072261	A	20231215	IN 2023-47072261	20231023

PRIORITY APPLN. INFO.:

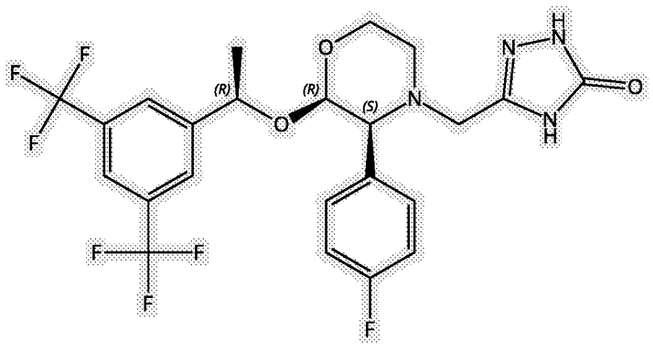
US 2021-63166995	P	20210327
US 2022-63269330	P	20220314
US 2022-17656702	A1	20220328
WO 2022-EP58180	W	20220328

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
US 20220305125	A1	Alive	20221006
CA 3212583	A1	Alive	20231005
WO 2022207580	A2	Alive	20221013
WO 2022207580	A3	Alive	20230112
AU 2022248850	A1	Alive	20231116
EP 4312978	A2	Alive	20240208
WO 2023174948	A2	Alive	20230928

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASFORMULTNS 2022:2496852
AB The present specification discloses pharmaceutical compn. disclosed herein comprises one or more therapeutic compds., one or more glycerolipids, and one or more digestion enhancers. The disclosed glycerolipids comprise one or more hard fats and one or more liq. fats. The disclosed digestion enhancers comprise one or more bile acids, one or more phospholipids, one or more free C14-24 fatty acids, one or more free C14-24 fatty acid surfactants, or any combination thereof. The present specification also discloses methods and procedures to formulate the disclosed one or more therapeutic compds. into the disclosed pharmaceutical compns.
IPCI A61K0047-14 [I]; A61K0047-28 [I]; A61K0031-12 [I]; A61K0031-216 [I]; A61K0031-05 [I]; A61K0031-58 [I]; A61K0031-7135 [I]; A61K0031-192 [I]; A61K0031-553 [I]; A61K0031-4418 [I]; A61K0031-4453 [I]; A61K0031-196 [I]; A61K0031-44 [I]; A61K0031-4184 [I]; A61K0031-436 [I]; A61K0031-5377 [I]; A61K0031-502 [I]; A61K0031-496 [I]; A61K0031-4025 [I]; A61K0038-12 [I]
IPCR A61K0047-14 [I]; A61K0031-05 [I]; A61K0031-12 [I]; A61K0031-192 [I]; A61K0031-196 [I]; A61K0031-216 [I]; A61K0031-4025 [I]; A61K0031-4184 [I]; A61K0031-436 [I]; A61K0031-44 [I]; A61K0031-4418 [I]; A61K0031-4453 [I]; A61K0031-496 [I]; A61K0031-502 [I]; A61K0031-5377 [I]; A61K0031-553 [I]; A61K0031-58 [I]; A61K0031-7135 [I]; A61K0038-12 [I]; A61K0047-28 [I]
CC 63-6 (Pharmaceuticals)

Section cross-reference(s): 1
IT Bile acids
Fats and Glyceridic oils
Fatty acids
Glycerolipids
Lecithins
Monoglycerides
Phospholipids
Polyoxyalkylenes
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. having improved bioavailability of therapeutics)
IT 458-37-7, Curcumin 4394-00-7, Niflumic acid 15307-79-6, Diclofenac sodium 15307-86-5, Diclofenac 15687-27-1, Ibuprofen 22204-53-1, Naproxen 31121-93-4 31431-39-7, Mebendazole 34031-32-8, Auranofin 53179-13-8, Pirfenidone 68302-57-8, Amlexanox 88170-10-9, Diclofenac calcium 120685-11-2, Midostaurin 130308-48-4, Icatibant 144701-48-4, Telmisartan 154229-19-3, Abiraterone 170729-80-3, Aprepitant 362665-56-3, Pitolisant 491833-29-5, Eliglustat 656247-17-5, Nintedanib 763113-22-0, Olaparib
RL: PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. having improved bioavailability of therapeutics)
IT 170729-80-3, Aprepitant
RL: PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. having improved bioavailability of therapeutics)
RN 170729-80-3 CAPLUS
CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
AU 2022248850 A1	AU 2022-248850	Register
CA 3212583 A1	CA 2022-3212583	Register
EP 4312978 A2	EP 2022-718916	Register|Federated Reg.
IN 202347072261 A	IN 2023-47072261	Register
KR 2024021751 A	KR 2023-7037012	Register|Global Dossier
US 20220305125 A1	US 2022-17656702	Register|Global Dossier
US 20240075147 A1	US 2023-18487486	Register|Global Dossier
WO 2022207580 A2	WO 2022-EP58180	Register|Global Dossier
WO 2022207580 A3	WO 2022-EP58180	Register|Global Dossier
WO 2023174948 A2	WO 2023-EP56506	Register|Global Dossier
WO 2023174948 A3	WO 2023-EP56506	Register|Global Dossier

L4 ANSWER 5 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN

ACCESSION NUMBER: 2022:2221248 CAPLUS Full-text
DOCUMENT NUMBER: 181:431761
TITLE: Small scale in vitro method to determine a potential bioequivalent equilibrium solubility range for fed human intestinal fluid
AUTHOR(S): Ines Silva, Maria; Khadra, Ibrahim; Pyper, Kate; Halbert, Gavin W.
CORPORATE SOURCE: Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, 161 Cathedral Street, Glasgow, G4 0RE, UK
SOURCE: European Journal of Pharmaceutics and Biopharmaceutics (2022), 177, 126-134
CODEN: EJPBEL; ISSN: 0939-6411
DIGITAL OBJECT ID: 10.1016/j.ejpb.2022.06.005
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English

AB Intestinal drug soly. is a key parameter controlling oral absorption but varies both intra and inter individuals and between the fasted and fed states, with food intake known to alter the bioavailability of many compds. Intestinal soly. can be measured in vitro either using sampled fed human intestinal fluid (FeHIF) or simulated fed intestinal fluid (SIF) but neither approach is optimal. FeHIF is difficult to obtain and variable, while for fed SIF multiple recipes are available with no consensus on the ideal version. A recent study characterised FeHIF aspirates using a multidimensional approach and calcd. nine simulated media recipes that covered over ninety percent of FeHIF compositional variability. In this study the equil. soly. of thirteen drugs have been measured using the nine simulated media recipes and compared to multiple previous design of expt. (DoE) studies, which have examd. the impact of fed SIF media components on soly. The measured nine media soly. data set is only statistically equiv. to the large scale 92 media DoE in 4 out of 13 drug comparisons, but has improved equivalence against small scale DoEs (9 or 10 media) with 6 out of 9 or 10 out of 12 (9 and 10 media resp.) equiv. Selective removal of non-biorelevant compns. from the 92 media DoE improves statistical equivalence to 9 out of 13 comparisons. The results indicate that soly. equivalence is linked to media component concns. and compns., the nine media system is measuring a similar soly. space to previous systems, with a narrower soly. range than the 92 point DoE but equiv. to smaller DoE systems. Phenytoin and tadalafil display a narrow soly. range, a behavior consistent with previous studies in fed and fasted states and only revealed through the multiple media approach. Custom DoE anal. of the nine media results to det. the most statistically significant component influencing soly. does not detect significant components. Indicating that the approach has a low statistical resoln. and is not appropriate if detn. of media component significance is required. This study demonstrates that it is possible to assess the fed intestinal equil. soly. envelope using the nine media recipes obtained from a multi-dimensional anal. of fed HIF. The derivation of the nine media compns. coupled with the results in this study indicate that the soly. results are more likely to reflect the fed intestinal soly. envelope than previous DoE studies and highlight that the system is worthy of further investigation.

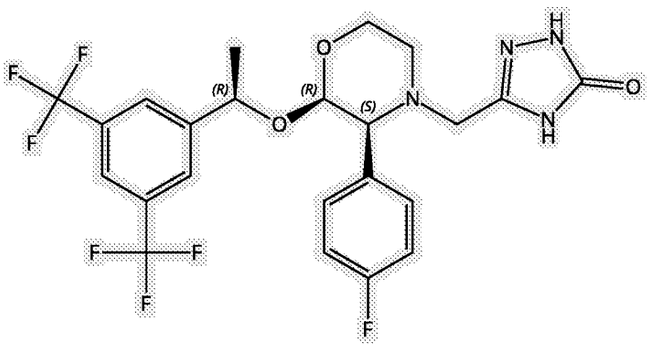
CC 63-6 (Pharmaceuticals)

IT Lecithins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(small scale in vitro method to det. potential bioequivalent equil. soly. range for fed human intestinal fluid)

IT 53-86-1 57-41-0 57-88-5, Cholest-5-en-3-ol (3β)-, biological studies 110-16-7, 2-Butenedioic acid (2Z)-, biological studies 111-03-5 112-80-1, 9-Octadecenoic acid (9Z)-, biological studies 145-42-6 14265-44-2, Phosphate, biological studies 15687-27-1 23288-49-5 25614-03-3 49562-28-9 72509-76-3 72956-09-3 84625-61-6 107753-78-6 137862-53-4 170729-80-3 171596-29-5
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(small scale in vitro method to det. potential bioequivalent equil. soly. range for fed human intestinal fluid)

IT 170729-80-3
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(small scale in vitro method to det. potential bioequivalent equil. soly. range for fed human intestinal fluid)

RN 170729-80-3 CAPLUS
CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 6 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2022:1355958 CAPLUS Full-text
DOCUMENT NUMBER: 179:75293
TITLE: Stable antiemetic emulsions
INVENTOR(S): Bhagwatwar, Harshal Prabhakar; Nerurkar, Manoj
PATENT ASSIGNEE(S): Steps BioSciences, Inc., USA
ULTIMATE OWNER: STEPS BIOSCIENCES
ULTIMATE OWNER STANDARD: STEPS BIOSCIENCES
SOURCE: U.S. Pat. Appl. Publ., 11pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

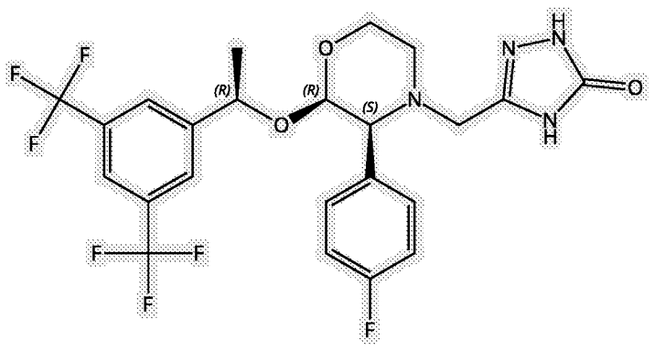
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20220160722	A1	20220526	US 2021-17531216	20211119
PRIORITY APPLN. INFO.:			IN 2020-41050531 A	20201120

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
US 20220160722	A1	Alive	20220609

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASFORMULTNS 2022:1355958
AB Emulsion formulations and systems for the i.v. or parenteral administration. of neurokinin-1 (NK-1) receptor antagonists for treatment of emesis are provided. Methods for prepg. the stable NK-1 receptor antagonist emulsions and pharmaceutical formulations are further provided. The emulsion formulations are prepd. and characterized as a formulation and process that will allow an NK-1 receptor antagonist compd. to be incorporated into an emulsion for i.v. injection and remain stable during the shelf life of the formulation. Specifically, emulsion formulations have an oil phase that includes oil, ethanol, egg lecithin , and the further addn. of sodium oleate that is mixed with an aq. phase and processed to form the emulsion formulation.
IPCI A61K0031-5377 [I]; A61K0009-00 [I]; A61K0009-107 [I]; A61K0047-24 [I]; A61K0047-12 [I]; A61K0047-10 [I]; A61K0047-44 [I]
IPCR A61K0031-5377 [I]; A61K0009-00 [I]; A61K0009-107 [I]; A61K0047-10 [I]; A61K0047-12 [I]; A61K0047-24 [I]; A61K0047-44 [I]
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1

IT Castor oil
Coconut oil
Corn oil
Cottonseed oil
Egg yolk lecithins
Lecithins
Olive oil
Safflower oil
Sesame oil
Soybean oil
Triglycerides
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(stable antiemetic emulsions)
IT 57-50-1, Sucrose, biological studies 64-17-5, Ethanol, biological studies 111-62-6, Ethyl oleate 143-19-1, Sodium oleate 303-43-5, Cholesteryl oleate 544-35-4, Ethyl linoleate 604-33-1, Cholesteryl linoleate 37220-82-9, Glyceryl oleate 37348-65-5, Glyceryl linoleate 136745-48-7, Octyl glycerate 152167-64-1, Decyl glycerate 170729-80-3, Aprepitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(stable antiemetic emulsions)
IT 170729-80-3, Aprepitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(stable antiemetic emulsions)
RN 170729-80-3 CAPLUS
CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
US 20220160722 A1	US 2021-17531216	Register|Global Dossier

L4 ANSWER 7 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2022:139737 CAPLUS Full-text
DOCUMENT NUMBER: 177:284905
TITLE: Pharmaceutical emulsion comprising an aprepitant, pharmaceutical injections, and methods of preparing emulsions
INVENTOR(S): Amano, Yohei; Katagiri, Kazumi
PATENT ASSIGNEE(S): Kewpie Corporation, Japan; FBC (Shanghai) Pharmaceutical Technology Co., Ltd.
ULTIMATE OWNER: FBC SHANGHAI PHARMACEUTICAL TECHNOLOGY; FBC SHANGHAI PHARMACEUTICAL TECH; FUBICHENG SHANGHAI MEDICAL TECH; KEWPIE CORPORATION
ULTIMATE OWNER STANDARD: FBC SHANGHAI PHARMACEUTICAL TECHNOLOGY; FBC SHANGHAI PHARMACEUTICAL TECH; FUBICHENG SHANGHAI MEDICAL TECH; Kewpie Corp
SOURCE: PCT Int. Appl., 28pp.; Chemical Indexing Equivalent to

174:540291 (JP)
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2022014113	A1	20220120	WO 2021-JP15552	20210415
JP 6832468	B1	20210224	JP 2020-121438	20200715
JP 2022018370	A	20220127		
CA 3187858	A1	20220120	CA 2021-3187858	20210415
KR 2023040956	A	20230323	KR 2022-7045138	20210415
EP 4169515	A1	20230426	EP 2021-843280	20210415
US 20230310443	A1	20231005	US 2023-18015492	20230110

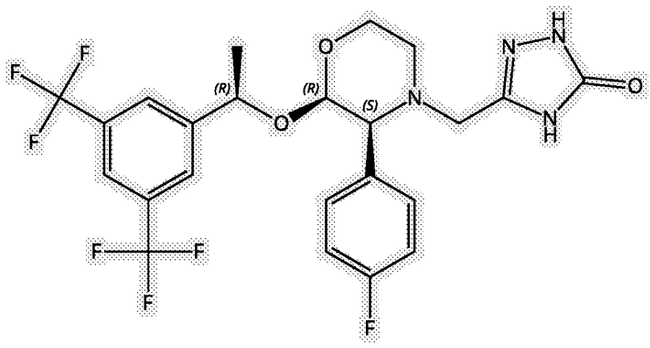
PRIORITY APPLN. INFO.: JP 2020-121438 A 20200715
WO 2021-JP15552 W 20210415

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
WO 2022014113	A1	Alive	20220203
JP 6832468	B1	Alive	20210304
JP 2022018370	A	Alive	20220224
CA 3187858	A1	Alive	20230216
KR 2023040956	A	Alive	20230420
EP 4169515	A1	Alive	20230427
US 20230310443	A1	Alive	20231012

AB The present invention pertains to an emulsion which contains an aprepitant, an emulsifier, an oil, a polyethylene glycol having an av. mol. wt. of 260-1100, and water, and to which ethanol is substantially not added. The content of the aprepitant is 0.50-0.90 w/v% based on the total amt., and the content of the emulsifier is 12.0-18 w/v%. The content of oil is 7.0-12.0 w/v %, and the content of polyethylene glycol is 0.5-10.0 w/v %. The av. particle diam. of the emulsion is 60-140 nm. According to the present invention, provided is an aprepitant-contg. emulsion having excellent stability without substantially adding ethanol.

IPCI A61K0031-5377 [I]; A61K0009-107 [I]; A61K0047-10 [I]; A61K0047-24 [I]; A61K0047-44 [I]; A61P0001-08 [I]
IPCR A61K0031-5377 [I]; A61K0009-107 [I]; A61K0047-10 [I]; A61K0047-24 [I]; A61K0047-44 [I]; A61P0001-08 [I]
CC 63-6 (Pharmaceuticals)
IT Egg yolk lecithins
Phospholipids
Polyoxyalkylenes
Soybean oil
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical emulsion comprising aprepitant, pharmaceutical injections, and methods of prepg. emulsions)
IT 170729-80-3
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical emulsion comprising aprepitant, pharmaceutical injections, and methods of prepg. emulsions)
IT 170729-80-3
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical emulsion comprising aprepitant, pharmaceutical injections, and methods of prepg. emulsions)
RN 170729-80-3 CAPLUS
CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
CA 3187858 A1	CA 2021-3187858	Register
EP 4169515 A1	EP 2021-843280	Register|Federated Reg.
JP 2022018370 A	JP 2020-121438	Register|Global Dossier
JP 6832468 B1	JP 2020-121438	Register|Global Dossier
KR 2023040956 A	KR 2022-7045138	Register|Global Dossier
US 20230310443 A1	US 2023-18015492	Register|Global Dossier
WO 2022014113 A1	WO 2021-JP15552	Register|Global Dossier

L4 ANSWER 8 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2021:2591917 CAPLUS Full-text
DOCUMENT NUMBER: 177:123225
TITLE: Preparation method of aprepitant emulsion injection for preventing nausea and emesis
INVENTOR(S): Guo, Shuer; Qin, Zhijun
PATENT ASSIGNEE(S): Guangzhou Manxiang Pharmaceutical Co., Ltd., Peop. Rep. China
ULTIMATE OWNER: GUANGZHOU MAXENMED MEDICINE
ULTIMATE OWNER STANDARD: GUANGZHOU MAXENMED MEDICINE
SOURCE: Faming Zhuanli Shenqing, 9pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

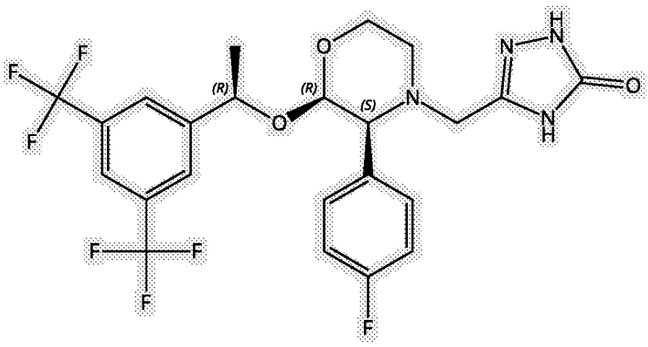
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 113712915	A	20211130	CN 2021-10018100	20210107

PRIORITY APPLN. INFO.: CN 2021-10018100 20210107
PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
CN 113712915	A	Alive	20211209

OTHER SOURCE(S): CASFORMULTNS 2021:2591917
AB The invention aprepitant emulsion injection is prepd. from (by wt%) aprepitant 0.2-1.2, pH regulator 0.25-0.75, permeation pressure regulator 3-8, injection water 56-75, emulsifier 12-15, cosolvent 2-5, and injection oil 5-15. The emulsifier is hydrogenated soybean lecithin or hydrogenated soybean phosphatidylcholine. The pH regulator is sodium hydroxide, sodium citrate, sodium dihydrogen phosphate or sodium oleate. The permeation pressure regulator is xylitol, sorbitol, mannitol or sucrose. The cosolvent is ethanol, glycerol, propylene glycol and polyethylene glycol. The injection oil is soybean oil, peanut oil, hydrogenated corn oil, triglyceride, medium-chain triglyceride, sesame oil and/or sunflower seed oil. By controlling content of emulsifier and shearing rotation speed, homogenization pressure and homogenization temp. in emulsion prepn. process, the invention preps. aprepitant emulsion injection with good oxidn. resistance and emulsification effect, and has

operability, simple process and low device loss.
IPCI A61K0009-107; A61K0047-24; A61K0031-5377; A61P0001-08; A61P0035-00
IPCR A61K0009-107 [I]; A61K0031-5377 [I]; A61K0047-24 [I]; A61P0001-08 [I]; A61P0035-00 [I]
CC 63-6 (Pharmaceuticals)
IT Corn oil
Soya lecithins
RL: MOA (Modifier or additive use); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hydrogenated; prepn. method of aprepitant emulsion injection for preventing nausea and emesis)
IT 170729-80-3, Aprepitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. method of aprepitant emulsion injection for preventing nausea and emesis)
IT 170729-80-3, Aprepitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. method of aprepitant emulsion injection for preventing nausea and emesis)
RN 170729-80-3 CAPLUS
CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
CN 113712915 A	CN 2021-10018100	Register|Global Dossier

L4 ANSWER 9 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2021:1541826 CAPLUS Full-text
DOCUMENT NUMBER: 175:329880
TITLE: Aprepitant ready-to-use injection emulsion compositions
INVENTOR(S): Akasapu, Prem Sagar; Subramanian, Veerappan; Subramanian, Ilango
PATENT ASSIGNEE(S): Somerset Therapeutics LLC, USA
ULTIMATE OWNER: SOMERSET THERAPEUTICS LLC
ULTIMATE OWNER STANDARD: SOMERSET THERAPEUTICS LLC
SOURCE: U.S. Pat. Appl. Publ., 8pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 20210212933	A1	20210715	US 2021-17147556		20210113
US 11517522	B2	20221206			
PRIORITY APPLN. INFO.:			US 2020-62961039	P	20200114

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
US 20210212933	A1	Alive	20210722
US 11517522	B2	Alive	20221215

OTHER SOURCE(S): CASFORMULTNS 2021:1541826

AB The present invention provides an emulsion compn. comprising aprepitant for treatment of emesis. Particularly, the invention is a ready-to-use emulsion compns. comprising aprepitant and medium chain triglycerides for administration by i.v. infusion, wherein the emulsion compn. is also free of ethanol. Further, the invention also provides processes of prepg. such compns. and their use for the prevention and control of acute and delayed chemotherapy-induced nausea and vomiting, and/or for prevention of postoperative nausea and vomiting.

IPCI A61K0009-00 [I]; A61K0009-107 [I]; A61K0047-14 [I]; A61M0005-24 [I]; A61K0031-5377 [I]; A61K0009-00 [I]; A61K0047-14 [I]; A61K0009-107 [I]; A61K0031-5377 [I]; A61M0005-24 [I]

IPCR A61K0009-00 [I]; A61K0009-107 [I]; A61K0031-5377 [I]; A61K0047-14 [I]; A61M0005-24 [I]

CC 63-6 (Pharmaceuticals)

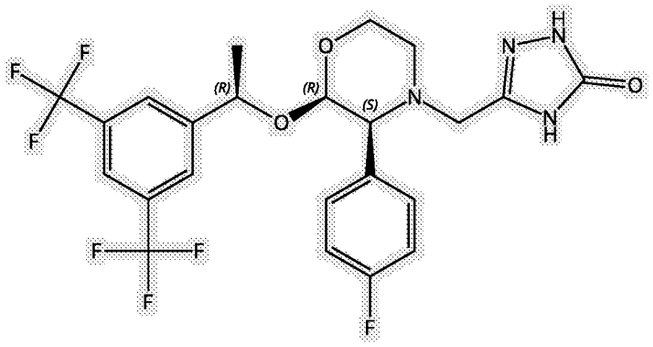
IT Lecithins
Medium-chain glycerides
Polyoxyalkylenes
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aprepitant ready-to-use injection emulsion compns.)

IT 170729-80-3, Aprepitant
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aprepitant ready-to-use injection emulsion compns.)

IT 170729-80-3, Aprepitant
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aprepitant ready-to-use injection emulsion compns.)

RN 170729-80-3 CAPLUS

CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
US 11517522 B2	US 2021-17147556	Register|Global Dossier
US 20210212933 A1	US 2021-17147556	Register|Global Dossier

L4 ANSWER 10 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN

ACCESSION NUMBER: 2021:685825 CAPLUS Full-text

DOCUMENT NUMBER: 178:140851

TITLE: Aprepitant submicroemulsion injection capable of being autoclaved, and its preparation method

INVENTOR(S): Qin, Linghao; Li, Yusheng; Zhu, Wanye; Wang, Wanting

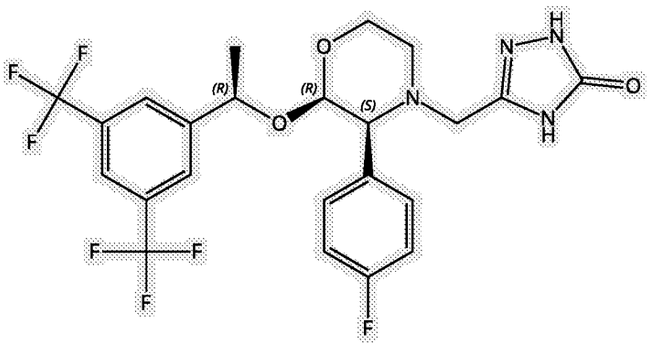
PATENT ASSIGNEE(S): Guangdong Pharmaceutical University, Peop. Rep. China
SOURCE: Faming Zhuanli Shenqing, 19pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 112535661	A	20210323	CN 2020-11524237	20201222
CN 112535661	B	20230407		

PRIORITY APPLN. INFO.: CN 2020-11524237 20201222
PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
CN 112535661	A	Alive	20210408
CN 112535661	B	Alive	20230427

OTHER SOURCE(S): CASFORMULTNS 2021:685825
AB A safe aprepitant submicroemulsion injection capable of being autoclaved having high efficiency, good stability and sterilization effect, and wide application in medicine field is provided. The aprepitant submicroemulsion injection comprises: polyethylene glycol 15hydroxystearate, phospholipids, aprepitant, oil for injection, emulsifier, co-emulsifier, solubilizer, stabilizer, isotonic agent, pH regulator and water for injection. The prepn. method comprises the following steps: (1) mixing aprepitant, injection oil and solubilizer, dissolving and dispersing with alc., and removing the alc. to obtain an oil phase mixt.; (2) stirring and mixing the emulsifier, co-emulsifier, stabilizer, isotonic agent and water for injection, and heat to dissolve to obtain the water phase mixt.; and (3) adding the oil phase mixt. to the water phase mixt., prepg. the emulsion, and autoclaving to obtain the aprepitant submicroemulsion injection. The aprepitant submicroemulsion injection is used in the prepn. of a medicine for treating nausea and vomiting.
IPCI A61K0009-107; A61K0031-5377; A61K0047-24; A61K0047-14; A61K0047-18; A61P0001-08; A61L0002-07
IPCR A61K0009-107 [I]; A61K0031-5377 [I]; A61K0047-14 [I]; A61K0047-18 [I]; A61K0047-24 [I]; A61L0002-07 [I]; A61P0001-08 [I]
CC 63-6 (Pharmaceuticals)
IT Amino acids
Egg yolk lecithins
Oils
Phospholipids
RL: MOA (Modifier or additive use); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aprepitant submicroemulsion injection capable of being autoclaved, and its prepn. method)
IT 56-41-7, L-Alanine, biological studies 56-84-8, L-Aspartic acid, biological studies 56-86-0, L-Glutamic acid, biological studies 63-91-2, L-Phenylalanine, biological studies 73-32-5, L-Isoleucine, biological studies 170729-80-3, Aprepitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aprepitant submicroemulsion injection capable of being autoclaved, and its prepn. method)
IT 170729-80-3, Aprepitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aprepitant submicroemulsion injection capable of being autoclaved, and its prepn. method)
RN 170729-80-3 CAPLUS
CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
CN 112535661 A	CN 2020-11524237	Register|Global Dossier
CN 112535661 B	CN 2020-11524237	Register|Global Dossier

L4 ANSWER 11 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2021:481715 CAPLUS Full-text
DOCUMENT NUMBER: 174:540291
TITLE: Pharmaceutical emulsion comprising an aprepitant, pharmaceutical injections, and methods of preparing emulsions
INVENTOR(S): Amano, Yohei; Katagiri, Kazumi
PATENT ASSIGNEE(S): Kewpie Corporation, Japan; FBC (Shanghai) Pharmaceutical Technology Co., Ltd.
ULTIMATE OWNER: KEWPIE CORPORATION; FBC SHANGHAI PHARMACEUTICAL TECH; FUBICHENG SHANGHAI MEDICAL TECH; FBC SHANGHAI PHARMACEUTICAL TECHNOLOGY
ULTIMATE OWNER STANDARD: Kewpie Corp; FBC SHANGHAI PHARMACEUTICAL TECH; FUBICHENG SHANGHAI MEDICAL TECH; FBC SHANGHAI PHARMACEUTICAL TECHNOLOGY
SOURCE: Jpn. Tokkyo Koho, 15pp.; Chemical Indexing Equivalent to 177:284905 (WO)
CODEN: JTXXFF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 6832468	B1	20210224	JP 2020-121438	20200715
JP 2022018370	A	20220127		
CA 3187858	A1	20220120	CA 2021-3187858	20210415
WO 2022014113	A1	20220120	WO 2021-JP15552	20210415
KR 2023040956	A	20230323	KR 2022-7045138	20210415
EP 4169515	A1	20230426	EP 2021-843280	20210415
CN 113952299	A	20220121	CN 2021-10772526	20210708
CN 117017915	A	20231110	CN 2023-11089804	20210708
US 20230310443	A1	20231005	US 2023-18015492	20230110

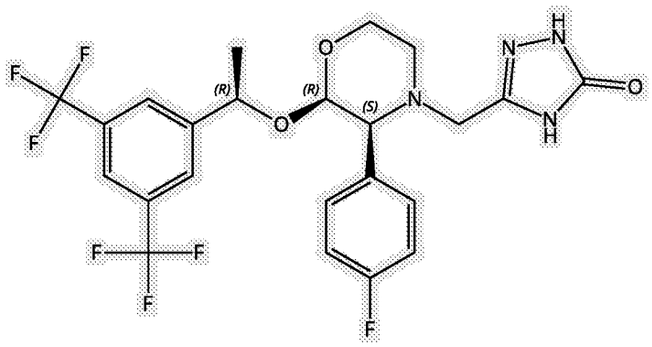
PRIORITY APPLN. INFO.:

JP 2020-121438	A	20200715
WO 2021-JP15552	W	20210415
CN 2021-10772526	A3	20210708

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
JP 6832468	B1	Alive	20210304
JP 2022018370	A	Alive	20220224
CA 3187858	A1	Alive	20230216
WO 2022014113	A1	Alive	20220203
KR 2023040956	A	Alive	20230420

EP 4169515 A1 Alive 20230427
CN 113952299 A Alive 20220203
CN 117017915 A Alive 20231116
US 20230310443 A1 Alive 20231012
OTHER SOURCE(S): CASFORMULTNS 2021:481715
AB The emulsion comprises: an aprepitant, an emulsifier, an oil, polyethylene glycol and water, with substantially no addn. of ethanol. The emulsion comprises a pH regulator and having a pH of 8.0-9.0. The content of the aprepitant is 0.50 w/v% or more and 0.90 w/v% or less based on the total amt., and the content of the emulsifier is 12.0 w/v% or more and 12.0 w/v% or more based on the total amt. The emulsion is 0 w/v% or less, the emulsion in which the emulsifier is a phospholipid. According to the present invention, provided is an aprepitant-contg. emulsion having excellent stability without substantially adding ethanol.
IPCI A61K0031-5377 [I]; A61K0009-107 [I]; A61P0001-08 [I]; A61K0047-10 [I]; A61K0047-24 [I]; A61K0047-44 [I]; A61K0009-107 [I]; A61K0047-10 [I]; A61K0031-5377 [I]; A61P0001-08 [I]; A61K0047-24 [I]; A61K0047-44 [I]
IPCR A61K0031-5377 [I]; A61K0009-107 [I]; A61K0047-10 [I]; A61K0047-24 [I]; A61K0047-44 [I]; A61P0001-08 [I]
CC 63-6 (Pharmaceuticals)
IT Egg yolk lecithins
Phospholipids
Polyoxyalkylenes
Soybean oil
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical emulsion comprising aprepitant, pharmaceutical injections, and methods of prepg. emulsions)
IT 170729-80-3
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical emulsion comprising aprepitant, pharmaceutical injections, and methods of prepg. emulsions)
IT 170729-80-3
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical emulsion comprising aprepitant, pharmaceutical injections, and methods of prepg. emulsions)
RN 170729-80-3 CAPLUS
CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

LINK INFORMATION

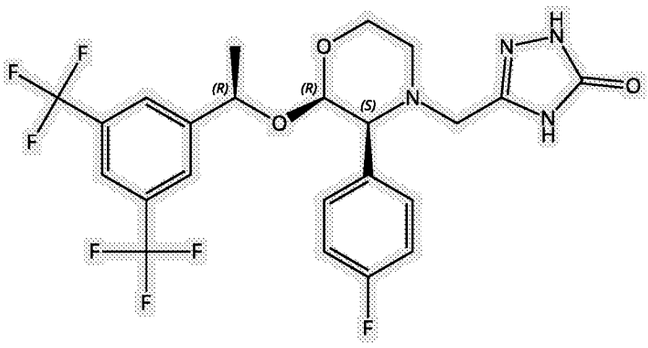
PUBLICATIONS	APPLICATIONS	REGISTER
CA 3187858 A1	CA 2021-3187858	Register
CN 113952299 A	CN 2021-10772526	Register|Global Dossier
CN 117017915 A	CN 2023-11089804	Register|Global Dossier

EP 4169515 A1	EP 2021-843280	Register|Federated Reg.
JP 2022018370 A	JP 2020-121438	Register|Global Dossier
JP 6832468 B1	JP 2020-121438	Register|Global Dossier
KR 2023040956 A	KR 2022-7045138	Register|Global Dossier
US 20230310443 A1	US 2023-18015492	Register|Global Dossier
WO 2022014113 A1	WO 2021-JP15552	Register|Global Dossier

L4 ANSWER 12 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2020:2334591 CAPLUS Full-text
DOCUMENT NUMBER: 174:387650
TITLE: Enhanced transdermal permeation of BCS class IV aprepitant using binary ethosome: Optimization, characterization and ex vivo permeation
AUTHOR(S): Abouhussein, Dalia M. N.
CORPORATE SOURCE: Department of Pharmaceutics, Egyptian Drug Authority Formerly Known As National Organization for Drug Control and Research (NODCAR), Egypt
SOURCE: Journal of Drug Delivery Science and Technology (2021), 61, 102185
CODEN: JDDSAL; ISSN: 1773-2247
DIGITAL OBJECT ID: 10.1016/j.jddst.2020.102185
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English

AB Aprepitant (APR) belongs to the Biopharmaceutics Classification System (BCS) class IV that is characterized by both low soly. and permeability. This study aims to develop a new transdermal APR nanovesicle for chemotherapy-induced nausea and vomiting. APR binary ethosomes (BEs) were developed using 32 factorial design where two independent variables namely; wt. of lecithin and propylene glycol were studied. The formulations were fully characterized through entrapment efficiency (EE), vesicle size (VS) and zeta potential (ZP). The optimized formulation was designated through the desirability value obtained by Design Expert program, visualized using transmission electron microscope (TEM) and studied for stability. Then the optimized formulation was incorporated in 0.8% carbopol 934 gel which was characterized and tested for in vitro and ex vivo release. F9 contg. 100 mg lecithin and 2.5 g propylene glycol was selected to be the optimum formulation. It showed desirability value of 0.958 as it displayed 89.6% EE, VS of 77 nm, -51.1 as ZP in addn. to adequate stability. The APR BE gel showed satisfactory phys., mech., rheol. and occlusive properties. The optimum formulation showed 4.9 folds higher permeation than APR suspension. BE gel exhibited a promising dosage form for the transdermal delivery of APR.

CC 63-5 (Pharmaceuticals)
IT Lecithins
Phospholipids
RL: MOA (Modifier or additive use); USES (Uses)
(optimum formulation of aprepitant binary ethosomes gel showed satisfactory phys., mech., rheol. and occlusive properties for transdermal delivery)
IT 170729-80-3
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(optimum formulation of aprepitant binary ethosomes gel showed satisfactory phys., mech., rheol. and occlusive properties for transdermal delivery)
IT 170729-80-3
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(optimum formulation of aprepitant binary ethosomes gel showed satisfactory phys., mech., rheol. and occlusive properties for transdermal delivery)
RN 170729-80-3 CAPLUS
CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

OS.CITING REF COUNT: 8 THERE ARE 8 CAPLUS RECORDS THAT CITE THIS RECORD (8 CITINGS)
REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 13 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2020:485442 CAPLUS Full-text
DOCUMENT NUMBER: 177:51750
TITLE: Aprepitant Intravenous Emulsion Based on Ion Pairing/Phospholipid Complex for Improving Physical and Chemical Stability During Thermal Sterilization
AUTHOR(S): Zhang, Xinyu; Wei, Ying; Cao, Zhijun; Xu, Ying; Lu, Cong; Zhao, Meiqi; Gou, Jingxin; Yin, Tian; Zhang, Yu; He, Haibing; Wang, Yanjiao; Tang, Xing
CORPORATE SOURCE: Department of Pharmaceutics, Shenyang Pharmaceutical University, Shenyang, Peop. Rep. China
SOURCE: AAPS PharmSciTech (2020), 21(3), 75
CODEN: AAPHFZ; ISSN: 1530-9932
DIGITAL OBJECT ID: 10.1208/s12249-019-1605-7
PUBLISHER: Springer
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
AB An aprepitant (APT) cholesteryl hemisuccinate (CHEMS) ion pair complex emulsion (AIPE) with high lecithin content was prepd. to improve sterilization stability through the film dispersion homogenization method; therefore, it could be a promising delivery system of APT. Medium-chain triglycerides (MCT) was selected as the oil phase to improve the soly. and stability of APT in oil phase. DSC, XRD, FT-IR, and 1H-NMR spectroscopies confirmed that the APT-CHEMS ion pair (AIP) was formed between CHEMS and APT. The formation of AIP significantly increased the hydrophobicity of APT, allowing it to be completely embedded in the oil phase core to improve chem. stability and decrease hydrolysis of APT in the water phase. Also, CHEMS had a strong affinity with lecithin and could stabilize lipid membranes, forming a stronger and thicker interface membrane to increase the phys. stability of AIPE. As a result, AIPE could withstand autoclaving at 120°C for 8 min without any change of particle size or content. Furthermore, AIPE with a potential of - 53.4 mV remained stable through spatial repulsion during sterilization. The encapsulation efficiency of AIPE was over 90% and the particle size was 106.8 ± 65.62 nm(0.286). Pharmacokinetic study in rats was comparable with that of CINVANTI which yielded a relative bioavailability of 114.31% indicating that the AIPE had similar pharmacokinetic processes in vivo with the analog of CINVANTI. The AUC0-t of the AIPE was 4.31-fold that of the APT soln.
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1
IT Egg yolk lecithins
Medium-chain glycerides
Soya lecithins
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

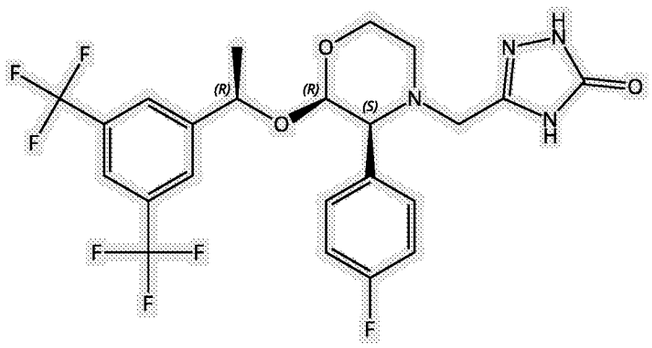
(aprepitant i.v. emulsion based on ion pairing/phospholipid complex for improving phys. and chem. stability during thermal sterilization)

IT 170729-80-3
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aprepitant i.v. emulsion based on ion pairing/phospholipid complex for improving phys. and chem. stability during thermal sterilization)

IT 170729-80-3
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aprepitant i.v. emulsion based on ion pairing/phospholipid complex for improving phys. and chem. stability during thermal sterilization)

RN 170729-80-3 CAPLUS

CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

OS.CITING REF COUNT: 6 THERE ARE 6 CAPLUS RECORDS THAT CITE THIS RECORD (6 CITINGS)

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 14 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN

ACCESSION NUMBER: 2020:456048 CAPLUS Full-text

DOCUMENT NUMBER: 177:51649

TITLE: Small scale design of experiment investigation of equilibrium solubility in simulated fasted and fed intestinal fluid

AUTHOR(S): McPherson, Stephanie; Perrier, Jeremy; Dunn, Claire; Khadra, Ibrahim; Davidson, Scott; Ainousah, Bayan; Wilson, Clive G.; Halbert, Gavin

CORPORATE SOURCE: Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow, G4 0RE, UK

SOURCE: European Journal of Pharmaceutics and Biopharmaceutics (2020), 150, 14-23
CODEN: EJPBEL; ISSN: 0939-6411

DIGITAL OBJECT ID: 10.1016/j.ejpb.2020.01.016

PUBLISHER: Elsevier B.V.

DOCUMENT TYPE: Journal; (online computer file)

LANGUAGE: English

AB It is widely recognized that drug soly. within the gastrointestinal tract (GIT) differs from values detd. in a simple aq. buffer and to circumvent this problem measurement in biorelevant fluids is detd. Biorelevant fluids are complex mixts. of components (sodium taurocholate, lecithin, sodium phosphate, sodium chloride, pancreatin and sodium oleate) at various concns. and pH levels to provide systems simulating fasted (FaSSIF) or fed (FeSSIF) intestinal media. Design of Expt. (DoE) studies have been applied to investigate FaSSIF and FeSSIF and indicate that a drugs equil. soly. varies over orders of magnitude, is influenced by the drug type and individual or combinations of media components, with some of

these interactions being drug specific. Although providing great detail on the drug media interactions these studies are resource intensive requiring up to ninety individual expts. for FeSSIF. In this paper a low sample no. or reduced DoE system has been investigated by restricting components with minimal soly. impact to a single value and only investigating variations in the concns. of sodium taurocholate, lecithin, sodium oleate, pH and addnl. in the case of fed media, monoglyceride. This reduces the expts. required to ten (FaSSIF) and nine (FeSSIF). Twelve poorly sol. drugs (Ibuprofen, Valsartan, Zafirlukast, Indomethacin, Fenofibrate, Felodipine, Probucol, Tadalafil, Carvedilol, Aprepitant, Bromocriptine and Itraconazole) were investigated and the results compared to published DoE studies and literature soly. values in human intestinal fluid (HIF), FaSSIF or FeSSIF. The soly. range detd. by the reduced DoE is statistically equiv. to the larger scale published DoE results in over eighty five percent of the cases. The reduced DoE range also covers HIF, FaSSIF or FeSSIF literature soly. values. In addn. the reduced DoE provides lowest measured soly. values that agree with the published DoE values in ninety percent of the cases. However, the reduced DoE only identified single and in some cases none of the major components influencing soly. in contrast to the larger published DoE studies which identified multiple individual components and component interactions. The identification of significant components within the reduced DoE was also dependent upon the drug and system under investigation. The study demonstrates that the lower exptl. no. reduces statistical power of the DoE to resolve the impact of media components on soly. However, in a situation where only the soly. range is required the reduced DoE can provide the desired information, which will be of benefit during in vitro development studies. Further refinements are possible to extend the reduced DoE protocol to improve biorelevance and application into areas such as PBPK modeling.

CC 63-5 (Pharmaceuticals)

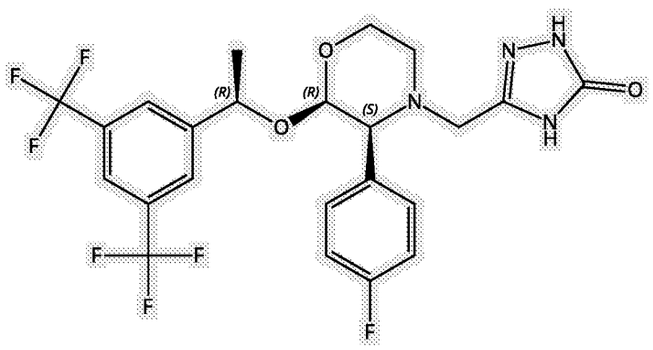
IT Lecithins
Monoglycerides
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(small scale design of expt. investigation of equil. soly. in simulated fasted and fed intestinal fluid)

IT 53-86-1 143-19-1 145-42-6 15687-27-1 23288-49-5 25614-03-3 49562-28-9 72509-76-3 72956-09-3 84625-61-6 107753-78-6 137862-53-4 170729-80-3 171596-29-5
RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(small scale design of expt. investigation of equil. soly. in simulated fasted and fed intestinal fluid)

IT 170729-80-3
RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(small scale design of expt. investigation of equil. soly. in simulated fasted and fed intestinal fluid)

RN 170729-80-3 CAPLUS

CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

OS.CITING REF COUNT: 16 THERE ARE 16 CAPLUS RECORDS THAT CITE THIS RECORD (16 CITINGS)
REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 15 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2020:418384 CAPLUS Full-text
DOCUMENT NUMBER: 172:285814
TITLE: Preparation of nanosuspension comprising nanocrystals of active pharmaceutical ingredients with little or no stabilizing agents
INVENTOR(S): Martin, Brice; Mignet, Nathalie; Corvis, Yohann
PATENT ASSIGNEE(S): Centre National de la Recherche Scientifique (CNRS), Fr.; Universite Paris Descartes; Institut National de la Sante et de la Recherche Medicale (INSERM); Ecole Nat Superieure de Chimie Paris
SOURCE: PCT Int. Appl., 66pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2020043735	A1	20200305	WO 2019-EP72873	20190827
EP 3616688	A1	20200304	EP 2018-306138	20180827
EP 3843705	A1	20210707	EP 2019-756406	20190827
EP 3843705	B1	20231129		
EP 3843705	C0	20231129		
US 20210315831	A1	20211014	US 2021-17269802	20210219

PRIORITY APPLN. INFO.: EP 2018-306138 A 20180827
WO 2019-EP72873 W 20190827

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
WO 2020043735	A1	Dead	20230427
EP 3616688	A1	Dead	20210909
EP 3843705	A1	Indeterminate	20231130
EP 3843705	B1	Indeterminate	20231130
EP 3843705	C0	Alive	20240215
US 20210315831	A1	Alive	20211121

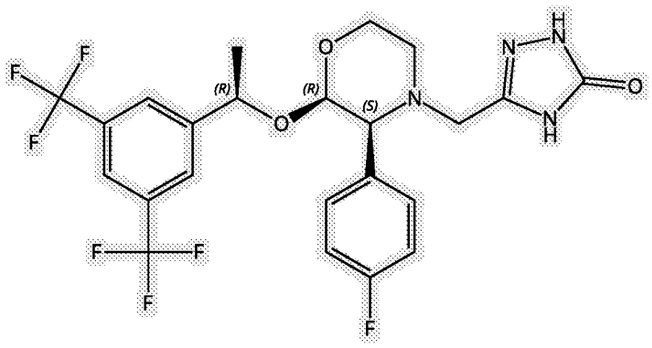
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
AB The invention relates to a method for manufg. a nanostructured powder comprising nanocryst. agglomerates contg. active pharmaceutical ingredient (API) in its cryst. form, said method comprising (i) Prepg. a first soln. comprising API and an API solvent; (ii) Mixing the first soln. with a second soln. comprising an API antisolvent and optionally a stabilizing agent P1 to obtain a third mixt.; (iii) Evapg. the third mixt. until both the API solvent and the API antisolvent are evapd., advantageously under vacuum; characterized in that when the stabilizing agent P1 is present, the third mixt. has a stabilizing agent P1 to API wt. ratio equal or less than 5, preferably less than 2. The invention also concerns a nanostructured powder and a nanosuspension.
IPCI A61K0009-14 [I]; A61K0009-51 [I]; A61K0031-365 [I]; A61K0031-7048 [I]; A61P0035-00 [I]
IPCR A61K0009-14 [I]; A61K0009-51 [I]; A61K0031-365 [I]; A61K0031-7048 [I]; A61P0035-00 [I]
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1
IT Albumins
Asialofetuins
Egg yolk lecithins
Lecithins
Soya phosphatidylcholines
Transferrins
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. of nanosuspension comprising nanocrystals of active pharmaceutical ingredients with little or no stabilizing agents)
IT 50-02-2, Dexamethasone 50-23-7, Hydrocortisone 50-24-8, Prednisolone 52-01-7, Spironolactone 53-86-1, Indometacin 61-68-7, Mefenamic acid 126-07-8, Griseofulvin 127-40-2, Lutein 137-66-6, Ascorbyl palmitate

153-18-4, Rutin 458-37-7, Curcumin 501-36-0, Resveratrol 520-33-2, Hesperetin 528-48-3, Fisetin 1198-77-2, Monosodium urate 1397-89-3, Amphotericin B 2030-63-9, Clofazimine 2608-24-4, Piposulfan 3681-99-0, Puerarin 7689-03-4, Camptothecin 10238-21-8, Glibenclamide 15307-86-5, Diclofenac acid 15687-27-1, Ibuprofen 17230-88-5, Danazol 19685-09-7, Hydroxycamptothecin 21967-41-9, Baicalin 22071-15-4, Ketoprofen 22204-53-1, Naproxen 22888-70-6, Silybin 22916-47-8, Miconazole 23214-92-8, Doxorubicin 28957-04-2, Oridonin 29990-52-1, Methyltryptophan 31431-39-7, Mebendazole 33069-62-4, Paclitaxel 49562-28-9, Fenofibrate 54965-21-8, Albendazole 59865-13-3, Cyclosporine 63675-72-9, Nisoldipine 66085-59-4, Nimodipine 71125-38-7, Meloxicam 73590-58-6, Omeprazole 73963-72-1, Cilostazole 79902-63-9, Simvastatin 80841-47-0, Asulacrine 83905-01-5, Azithromycin 84625-61-6, Itraconazole 88426-33-9, Buparvaquone 98093-93-7, Riccardin D 114977-28-5, Docetaxel 116122-36-2, Breviscapine 129722-12-9, Aripiprazole 141374-81-4, Tarazepide 145040-37-5, Candesartan cilexetil 146939-27-7, Ziprasidone 147362-57-0, Loviride 153559-49-0, Bexarotene 154598-52-4, Efavirenz 169590-42-5, Celecoxib 170729-80-3, Aprepitant 183133-96-2, Cabazitaxel 206361-99-1, Darunavir 330784-47-9, Avanafil 1257228-26-4, Amoitone B
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. of nanosuspension comprising nanocrystals of active pharmaceutical ingredients with little or no stabilizing agents)

IT 170729-80-3, Aprepitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. of nanosuspension comprising nanocrystals of active pharmaceutical ingredients with little or no stabilizing agents)

RN 170729-80-3 CAPLUS

CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
EP 3616688 A1	EP 2018-306138	Register|Federated Reg.
EP 3843705 A1	EP 2019-756406	Register|Federated Reg.
EP 3843705 B1	EP 2019-756406	Register|Federated Reg.
EP 3843705 C0	EP 2019-756406	Register|Federated Reg.
US 20210315831 A1	US 2021-17269802	Register|Global Dossier
WO 2020043735 A1	WO 2019-EP72873	Register|Global Dossier

L4 ANSWER 16 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2020:245679 CAPLUS Full-text
DOCUMENT NUMBER: 172:258881
TITLE: Emulsion containing high proportion emulsifier and preparation method thereof

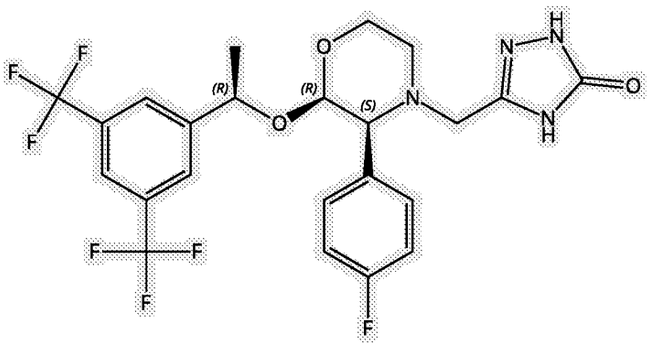
INVENTOR(S): Niu, Yawei; Xu, Wendong; Tang, Shunzhi; Yuan, Cheng; Fu, Yuping; Guan, Weijian; Wang, Guocai; Mou, Xiaonan; Li, Jirong; Li, Yao
PATENT ASSIGNEE(S): Guangzhou Baiyunshan Hanfang Pharmaceutical Co., Ltd., Peop. Rep. China
ULTIMATE OWNER: GUANGZHOU BAIYUNSHAN PHARMACEUTICAL HOLDINGS CO., LTD.
ULTIMATE OWNER STANDARD: Guangzhou Baiyunshan Pharma
SOURCE: Faming Zhuanli Shenqing, 15pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 110772482	A	20200211	CN 2019-11215436	20191202

PRIORITY APPLN. INFO.: CN 2019-11215436 20191202
PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
CN 110772482	A	Dead	20230511

AB The invention discloses an emulsion contg. high proportion emulsifier and prepn. method thereof, which has the advantages of high drug loading and high bioavailability. The emulsion contg. high proportion emulsifier comprises the following raw materials in percentage by wt.: oil phase solvent 10-30%, emulsifier 10-30%, co-emulsifier 1-5%, volatile assistant 1-5%, stabilizer 0.05-0.6%, isoosmotic adjusting agent 1-5%, viscosity regulator 1-10%, active pharmaceutical ingredient 1-5%, and the balance of injection water.
IPCI A61K0009-107; A61K0047-26; A61K0047-44; A61K0047-14; A61K0047-10; A61K0031-5377
IPCR A61K0009-107 [I]; A61K0031-5377 [I]; A61K0047-10 [I]; A61K0047-14 [I]; A61K0047-26 [I]; A61K0047-44 [I]
CC 63-7 (Pharmaceuticals)
IT Carbohydrates
Castor oil
Egg yolk lecithins
Fish oil
Fructooligosaccharides
Olive oil
Phosphatidylcholines
Phosphatidylglycerols
Soya lecithins
Soybean oil
Triglycerides
RL: MOA (Modifier or additive use); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(emulsion contg. high proportion emulsifier and prepn. method thereof)
IT 170729-80-3, Aprepitant 552292-08-7, Rolapitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(emulsion contg. high proportion emulsifier and prepn. method thereof)
IT 170729-80-3, Aprepitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(emulsion contg. high proportion emulsifier and prepn. method thereof)
RN 170729-80-3 CAPLUS
CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
CN 110772482 A	CN 2019-11215436	Register|Global Dossier

L4 ANSWER 17 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2019:1744396 CAPLUS Full-text
DOCUMENT NUMBER: 171:388517
TITLE: Aqueous formulations for insoluble drugs
INVENTOR(S): Chen, Andrew Xian; Islam, Mohammad Saiful; Chu, Jan-Jon; Xu, Jianmin
PATENT ASSIGNEE(S): USA
SOURCE: PCT Int. Appl., 84pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2019173526	A1	20190912	WO 2019-US21029	20190306
CA 3088017	A1	20190912	CA 2019-3088017	20190306
AU 2019231699	A1	20200716	AU 2019-231699	20190306
AU 2019231699	B2	20230309		
CN 111867562	A	20201030	CN 2019-80017435	20190306
CN 111867562	B	20230707		
EP 3761961	A1	20210113	EP 2019-764228	20190306
JP 2021515048	T	20210617	JP 2020-570411	20190306
US 20200368159	A1	20201126	US 2020-16993017	20200813
US 11541006	B2	20230103		

PRIORITY APPLN. INFO.: US 2018-62639710 P 20180307
WO 2019-US21029 W 20190306

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
WO 2019173526	A1	Dead	20221110
CA 3088017	A1	Alive	20201121
AU 2019231699	A1	Alive	20201121
AU 2019231699	B2	Alive	20230316
CN 111867562	A	Alive	20201120
CN 111867562	B	Alive	20230720
EP 3761961	A1	Alive	20210118
JP 2021515048	T	Alive	20210624
US 20200368159	A1	Alive	20221020
US 11541006	B2	Alive	20230119

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASFORMULTNS 2019:1744396
AB This invention relates to clear one-phase liq. formulation vehicles

comprising lecithin , MCT, bile salt and water. In an aspect, this invention provides a clear and one-phase aq. liq. compn. comprising: a lecithin , MCT, bile salt, and water, in a four-component LMBW compn., their prepn. and applications in drug formulations.

IPCI A61K0009-08 [I]; A61K0009-00 [I]; A61K0047-14 [I]; A61K0047-54 [I]

IPCR A61K0009-08 [I]; A61K0009-00 [I]; A61K0047-14 [I]; A61K0047-54 [I]

CC 63-6 (Pharmaceuticals)

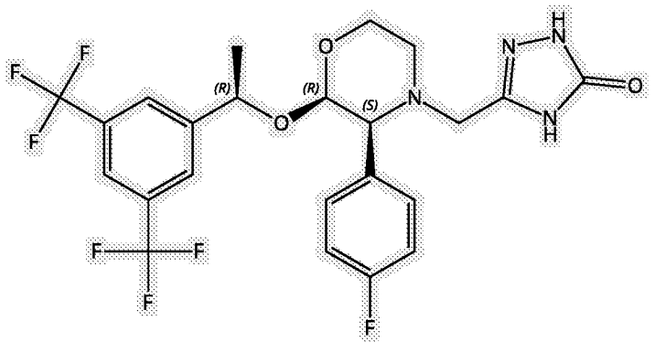
IT Bile salts
Egg yolk lecithins
Lecithins
Medium-chain glycerides
Polyoxyalkylenes
Sesame oil
Soya phosphatidylcholines
Soybean oil
Tocopherols
RL: MOA (Modifier or additive use); USES (Uses)
(aq. formulations for insol. drugs)

IT 52-21-1, Prednisolone Acetate 57-83-0, Progesterone, biological studies 59-92-7, Levodopa, biological studies 60-18-4, L-Tyrosine, biological studies 84-80-0, Phytonadione 501-36-0, Resveratrol 1951-25-3, Amiodarone 2078-54-8, Propofol 7553-56-2, Iodine, biological studies 7689-03-4, Camptothecin 12633-72-6, Amphotericin 15687-27-1, Ibuprofen 33069-62-4, Paclitaxel 59865-13-3, Cyclosporine 81103-11-9, Clarithromycin 84625-61-6, Itraconazole 100286-90-6, Irinotecan hydrochloride 169590-42-5, Celecoxib 170729-80-3, Aprepitant 171228-49-2, Posaconazole
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aq. formulations for insol. drugs)

IT 170729-80-3, Aprepitant
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aq. formulations for insol. drugs)

RN 170729-80-3 CAPLUS

CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
AU 2019231699 A1	AU 2019-231699	Register
AU 2019231699 B2	AU 2019-231699	Register
CA 3088017 A1	CA 2019-3088017	Register
CN 111867562 A	CN 2019-80017435	Register|Global Dossier
CN 111867562 B	CN 2019-80017435	Register|Global Dossier
EP 3761961 A1	EP 2019-764228	Register|Federated Reg.
JP 2021515048 T	JP 2020-570411	Register|Global Dossier
US 11541006 B2	US 2020-16993017	Register|Global Dossier

US 20200368159 A1 US 2020-16993017 Register|Global Dossier
WO 2019173526 A1 WO 2019-US21029 Register|Global Dossier

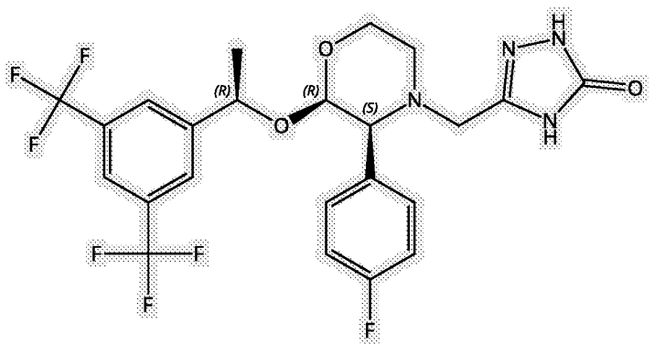
L4 ANSWER 18 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2019:1475315 CAPLUS Full-text
DOCUMENT NUMBER: 171:221789
TITLE: Method of administering emulsion formulations of an NK-1 receptor antagonist
INVENTOR(S): Ottoboni, Thomas B.; Quart, Barry D.
PATENT ASSIGNEE(S): Heron Therapeutics, Inc., USA
ULTIMATE OWNER: HERON THERAPEUTICS, INC.
ULTIMATE OWNER STANDARD: HERON THERAPEUTICS, INC.
SOURCE: U.S. Pat. Appl. Publ., 23pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 20190231688	A1	20190801	US 2019-16261459		20190129
WO 2019152430	A1	20190808	WO 2019-US15708		20190129
AU 2019214872	A1	20200806	AU 2019-214872		20190129
EP 3746051	A1	20201209	EP 2019-705044		20190129
JP 2021512091	T	20210513	JP 2020-541556		20190129
PRIORITY APPLN. INFO.:			US 2018-62624050	P	20180130
			WO 2019-US15708	W	20190129

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
US 20190231688	A1	Alive	20230914
WO 2019152430	A1	Dead	20220929
AU 2019214872	A1	Dead	20230803
EP 3746051	A1	Dead	20211117
JP 2021512091	T	Alive	20210520

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASFORMULTNS 2019:1475315
AB Disclosed herein are methods of administering pharmaceutical formulations of a neurokinin-1 (NK-1) receptor antagonist to a subject in need of treatment of emesis.
IPCI A61K0009-107 [I]; A61K0031-5377 [I]; A61K0009-00 [I]; A61K0047-24 [I]; A61K0031-573 [I]; A61K0047-44 [I]; A61K0047-10 [I]; A61K0047-12 [I]; A61K0047-26 [I]; A61K0031-496 [I]
IPCR A61K0009-107 [I]; A61K0009-00 [I]; A61K0031-496 [I]; A61K0031-5377 [I]; A61K0031-573 [I]; A61K0047-10 [I]; A61K0047-12 [I]; A61K0047-24 [I]; A61K0047-26 [I]; A61K0047-44 [I]
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1, 2
IT Alcohols
Egg yolk lecithins
Phospholipids
Soybean oil
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(method of administering emulsion formulations of NK-1 receptor antagonist)
IT 2392-39-4, Dexamethasone sodium phosphate 147116-64-1, Ezlopitant 147116-67-4, Maropitant 170729-80-3, Aprepitant 290296-68-3, Befetupitant 290297-26-6, Netupitant 334476-46-9, Vestipitant 414910-27-3, Casopitant 552292-08-7, Rolapitant 579475-18-6, Orvepitant 860642-69-9, Ser-lopitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(method of administering emulsion formulations of NK-1 receptor antagonist)
IT 170729-80-3, Aprepitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(method of administering emulsion formulations of NK-1 receptor antagonist)
RN 170729-80-3 CAPLUS
CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
AU 2019214872 A1	AU 2019-214872	Register
EP 3746051 A1	EP 2019-705044	Register|Federated Reg.
JP 2021512091 T	JP 2020-541556	Register|Global Dossier
US 20190231688 A1	US 2019-16261459	Register|Global Dossier
WO 2019152430 A1	WO 2019-US15708	Register|Global Dossier

L4 ANSWER 19 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2019:425605 CAPLUS Full-text
DOCUMENT NUMBER: 170:406568
TITLE: Aprepitant emulsion for treating nausea and vomiting after chemotherapy in tumor patient, and its preparation method and application
INVENTOR(S): Xu, Wendong; Tang, Shunzhi; Yuan, Cheng; Niu, Yawei; Fu, Yuping; Wang, Guocai; Guan, Weijian; Mou, Xiaonan; He, Jie; Li, Jirong; Yang, Yuqiong; Li, Yao
PATENT ASSIGNEE(S): Guangzhou Baiyunshan Hanfang Pharmaceutical Co., Ltd., Peop. Rep. China
ULTIMATE OWNER: GUANGZHOU BAIYUNSHAN PHARMACEUTICAL HOLDINGS CO., LTD.
ULTIMATE OWNER STANDARD: Guangzhou Baiyunshan Pharma
SOURCE: Faming Zhuanli Shenqing, 14pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

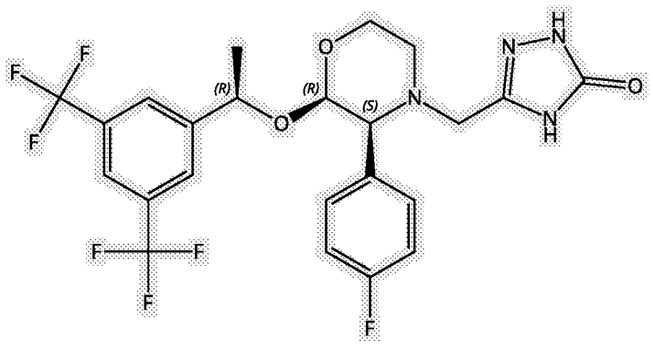
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 109432002	A	20190308	CN 2018-11587906	20181225

PRIORITY APPLN. INFO.: CN 2018-11587906 20181225
PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
CN 109432002	A	Dead	20220825

OTHER SOURCE(S): CASFORMULTNS 2019:425605
AB An aprepitant emulsion useful for reducing nausea and vomiting in the pre and post-chemotherapy of the tumor, improving immunity and nutritional support of the tumor patient, and reducing acute and delayed nausea and vomiting in high-dose cisplatin combined with high-dose sensitized cancer chemotherapy is provided. The aprepitant emulsion comprises the following components in mass %: 0.05-2.5 of aprepitant, 10-30 of oil phase solvent, 0.8-18 of emulsifier, 0.03-0.6 of stabilizer, 1-5 of isotonicity regulator, and further comprising a pH regulator, balance being purified water, where the pH of the emulsion is 5.5-8. The prepn. method comprises the following steps: (1) weighing the oil phase solvent, emulsifier and antioxidant, heating in a water bath, dissolving all the emulsifiers, and adding aprepitant and dissolving well to obtain an oil phase; (2) weighing

stabilizer, isotonicity regulator, pH regulator, adding to purified water, and heating in water bath to obtain water phase; (3) slowly adding the oil phase to the water phase, shearing at high speed under stirring, adding the remaining purified water with high speed stirring to obtain colostrum; (4) subjecting obtained colostrum to microfluidization to obtain a final emulsion; and (5) filling the colostrum with nitrogen, sealing and sterilizing in a rotary sterilizing pot to obtain an aprepitant emulsion.
IPCI A61K0009-107; A61K0031-5377; A23L0033-10; A23P0010-00; A61P0001-08; A61P0035-00
IPCR A61K0009-107 [I]; A23L0033-10 [I]; A23P0010-00 [I]; A61K0031-5377 [I]; A61P0001-08 [I]; A61P0035-00 [I]
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1
IT Egg yolk lecithins
Fatty acids
Phosphatidylcholines
Phosphatidylglycerols
Soya lecithins
Tocopherols
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aprepitant emulsion for treating nausea and vomiting after chemotherapy in tumor patient, and its prepn. method and application)
IT 50-99-7, D-Glucose, biological studies 56-81-5, Glycerin, biological studies 69-65-8, D-Mannitol 112-80-1, Oleic acid, biological studies 143-19-1, Sodium oleate 7631-90-5, Sodium bisulfite 7647-14-5, Sodium chloride, biological studies 7681-57-4, Sodium metabisulfite 7772-98-7, Sodium thiosulfate 9005-65-6, Polysorbate 80 106392-12-5, Poloxamer 170729-80-3, Aprepitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aprepitant emulsion for treating nausea and vomiting after chemotherapy in tumor patient, and its prepn. method and application)
IT 170729-80-3, Aprepitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aprepitant emulsion for treating nausea and vomiting after chemotherapy in tumor patient, and its prepn. method and application)
RN 170729-80-3 CAPLUS
CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
CN 109432002 A	CN 2018-11587906	Register|Global Dossier

L4 ANSWER 20 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2019:340286 CAPLUS Full-text
DOCUMENT NUMBER: 170:348016
TITLE: Aprepitant intravenous emulsion for treating chemotherapy-induced nausea and vomiting, and its

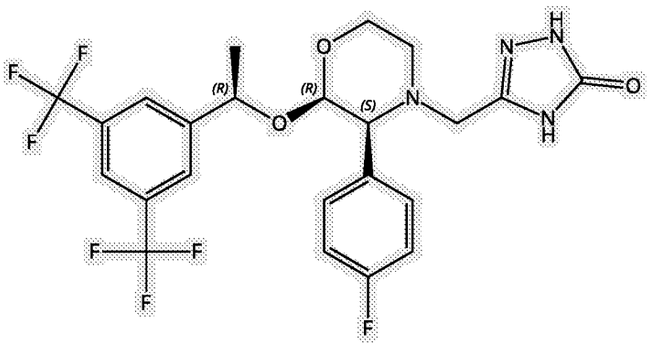
preparation method
INVENTOR(S): Yuan, Cheng; Xu, Wendong; Tang, Shunzhi; He, Jie; Niu, Yawei; Fu, Yuping; Wang, Guocai; Guan, Weijian; Mou, Xiaonan; Li, Yao
PATENT ASSIGNEE(S): Guangzhou Baiyunshan Hanfang Pharmaceutical Co., Ltd., Peop. Rep. China
ULTIMATE OWNER: GUANGZHOU BAIYUNSHAN PHARMACEUTICAL HOLDINGS CO., LTD.
ULTIMATE OWNER STANDARD: Guangzhou Baiyunshan Pharma
SOURCE: Faming Zhuanli Shenqing, 11pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 109364023	A	20190222	CN 2018-11588409	20181225

PRIORITY APPLN. INFO.: CN 2018-11588409 20181225
PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
CN 109364023	A	Transitional	20240222

OTHER SOURCE(S): CASFORMULTNS 2019:340286
AB The present invention relates to an i.v. emulsion contg. the following components by mass percentage: 0.05-3% of aprepitant, 5-30% of oil phase solvent, 1.2-18% of emulsifier, 0.03-0.6% of stabilizer, 1-5% of isotonicity adjusting agent, and 0.02-0.5% of antioxidant. The i.v. emulsion further contains a pH adjusting agent and water for injection, where the pH of the i.v. emulsion is 5.5-8.0. The i.v. emulsion has greatly improved the clin. safety, and is utilized for treating acute and delayed nausea and vomiting caused by high-dose cisplatin combined with high-dose sensitizing cancer chemotherapy and reducing nausea and vomiting in the early and middle stages of tumor chemotherapy.
IPCI A61K0009-107; A61K0047-24; A61K0047-12; A61K0031-5377; A61P0035-00; A61P0001-08
IPCR A61K0009-107 [I]; A61K0031-5377 [I]; A61K0047-12 [I]; A61K0047-24 [I]; A61P0001-08 [I]; A61P0035-00 [I]
CC 63-6 (Pharmaceuticals)
IT Castor oil
Egg yolk lecithins
Fish oil
Olive oil
Phosphatidylcholines
Phosphatidylglycerols
Soya phospholipids
Soybean oil
Teaseed oil
Tocopherols
RL: MOA (Modifier or additive use); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aprepitant i.v. emulsion for treating chemotherapy-induced nausea and vomiting, and its prepn. method)
IT 170729-80-3, Aprepitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aprepitant i.v. emulsion for treating chemotherapy-induced nausea and vomiting, and its prepn. method)
IT 170729-80-3, Aprepitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aprepitant i.v. emulsion for treating chemotherapy-induced nausea and vomiting, and its prepn. method)
RN 170729-80-3 CAPLUS
CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
CN 109364023 A	CN 2018-11588409	Register|Global Dossier

L4 ANSWER 21 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2018:2521745 CAPLUS Full-text
DOCUMENT NUMBER: 170:140265
TITLE: High stability aprepitant nano-emulsion and preparation method thereof
INVENTOR(S): Fu, Jifeng; Wang, Wenjuan; Guo, Jia; Zhang, Liancheng
PATENT ASSIGNEE(S): Beijing Ruiyue Biomedical Technology Co., Ltd., Peop. Rep. China
ULTIMATE OWNER: BEIJING RUIYUE BIOLOGY MEDICAL TECH
ULTIMATE OWNER STANDARD: BEIJING RUIYUE BIOLOGY MEDICAL TECH
SOURCE: Faming Zhuanli Shenqing, 9pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

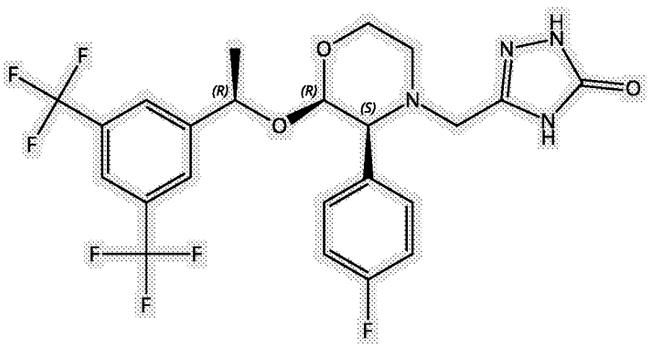
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 109010272	A	20181218	CN 2018-11133738	20180927

PRIORITY APPLN. INFO.: CN 2018-11133738 20180927
PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
CN 109010272	A	Dead	20230323

OTHER SOURCE(S): CASFORMULTNS 2018:2521745
AB The invention discloses a nano-emulsion of aprepitant as shown in structure I and prepn. method thereof. The nano-emulsion is prepd. with the following components in percentage by wt.: aprepitant 0.05-1.5%, soybean oil 2-20%, egg yolk lecithin 5-20%, ethanol 0.5-5%, sodium oleate 0.05-2%, sucrose 2-10%, and water for injection 40-80%. The sodium oleate is added into the oil phase to rapidly stabilize the oil droplets when contacts with the aq. phase, thereby increasing the stability of the nano-emulsion.
IPCI A61K0009-107; A61K0047-12; A61K0047-44; A61K0047-24; A61K0047-10; A61K0047-26; A61K0031-5377; A61P0001-08
IPCR A61K0009-107 [I]; A61K0031-5377 [I]; A61K0047-10 [I]; A61K0047-12 [I]; A61K0047-24 [I]; A61K0047-26 [I]; A61K0047-44 [I]; A61P0001-08 [I]
CC 63-6 (Pharmaceuticals)
IT Egg yolk lecithins
Soybean oil
RL: MOA (Modifier or additive use); NANO (Nanomaterial); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(High stability aprepitant nano-emulsion and prepn. method thereof)
IT 170729-80-3, Aprepitant
RL: NANO (Nanomaterial); THU (Therapeutic use); BIOL (Biological study);

USES (Uses)
(High stability aprepitant nano-emulsion and prepn. method thereof)
IT 170729-80-3, Aprepitant
RL: NANO (Nanomaterial); THU (Therapeutic use); BIOL (Biological study);
USES (Uses)
(High stability aprepitant nano-emulsion and prepn. method thereof)
RN 170729-80-3 CAPLUS
CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
CN 109010272 A	CN 2018-11133738	Register|Global Dossier

L4 ANSWER 22 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2018:2521716 CAPLUS Full-text
DOCUMENT NUMBER: 170:154781
TITLE: Fat emulsion injection of aprepitant with improved stability for treating chemotherapy-induced nausea and vomiting
INVENTOR(S): Liu, Jie; Liu, Yun; Zhou, Lili
PATENT ASSIGNEE(S): Fubicheng (Shanghai) Pharmaceutical Technology Co., Ltd., Peop. Rep. China
ULTIMATE OWNER: FUBICHENG SHANGHAI MEDICINE TECH
ULTIMATE OWNER STANDARD: FUBICHENG SHANGHAI MEDICINE TECH
SOURCE: Faming Zhuanli Shenqing, 11pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

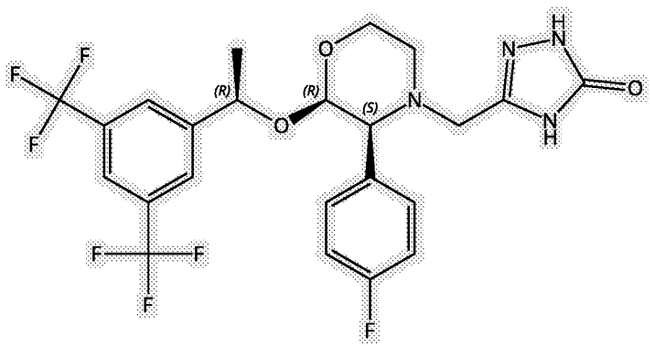
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 109010269	A	20181218	CN 2018-10979074	20180827
CN 109010269	B	20210420		
PRIORITY APPLN. INFO.:			CN 2018-10979074	20180827

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
CN 109010269	A	Alive	20201121
CN 109010269	B	Alive	20210430

OTHER SOURCE(S): CASFORMULTNS 2018:2521716
AB The title fat emulsion injection of aprepitant for treating chemotherapy-induced nausea and vomiting is prepd. from aprepitant, egg yolk lecithin , oil for injection (coconut oil, soybean oil, or olive oil), glycine, polyvinylpyrrolidone, water for injection, sodium oleate, and C1-5 short-chain alc. (ethanol or propanediol). The inventive prepn. has improved stability and reduced vascular irritation.

IPCI A61K0009-107; A61K0031-5377; A61K0047-18; A61K0047-32; A61K0031-439;
A61K0009-08; A61P0001-08
IPCR A61K0009-107 [I]; A61K0009-08 [I]; A61K0031-439 [I]; A61K0031-5377 [I];
A61K0047-18 [I]; A61K0047-32 [I]; A61P0001-08 [I]
CC 63-6 (Pharmaceuticals)
IT Egg yolk lecithins
RL: MOA (Modifier or additive use); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(Lipoid E 80; fat emulsion injection of aprepitant with improved stability for treating chemotherapy-induced nausea and vomiting)
IT 170729-80-3, Aprepitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(fat emulsion injection of aprepitant with improved stability for treating chemotherapy-induced nausea and vomiting)
IT 170729-80-3, Aprepitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(fat emulsion injection of aprepitant with improved stability for treating chemotherapy-induced nausea and vomiting)
RN 170729-80-3 CAPLUS
CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
CN 109010269 A	CN 2018-10979074	Register|Global Dossier
CN 109010269 B	CN 2018-10979074	Register|Global Dossier

L4 ANSWER 23 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2018:1210583 CAPLUS Full-text
DOCUMENT NUMBER: 169:118657
TITLE: Novel formulations of aprepitant
INVENTOR(S): Titley, Paul Charlton
PATENT ASSIGNEE(S): N4 Pharma UK Limited, UK
ULTIMATE OWNER: N4 PHARMA UK; N4 PHARMA
ULTIMATE OWNER STANDARD: N4 PHARMA UK; N4 PHARMA
SOURCE: PCT Int. Appl., 85pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2018115888	A1	20180628	WO 2017-GB53864		20171221
PRIORITY APPLN. INFO.:			GB 2016-21867	A	20161221
			GB 2017-16293	A	20171005

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE

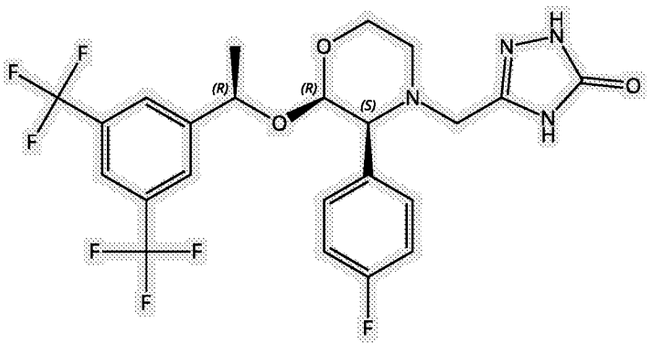
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WO 2018115888 A1 Dead 20210826
OTHER SOURCE(S): CASFORMULTNS 2018:1210583
AB The invention provides a pharmaceutical compn. which comprises: a first fraction comprising aprepitant; and a controlled-release fraction comprising aprepitant.
IPCI A61K0009-20 [I]; A61K0009-24 [I]; A61K0031-00 [I]
IPCR A61K0009-20 [I]; A61K0009-24 [I]; A61K0031-00 [I]
CC 63-1 (Pharmaceuticals)
IT Acrylic polymers
Activated charcoal
Alkali metal bicarbonates
Alkali metal carbonates
Carnauba wax
Fatty acids
Gelatins
Hydrogenated vegetable oils
Lecithins
Paraffin waxes
Polyoxyalkylenes
Polysaccharides
Shellac
Silica gel
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(novel formulations of aprepitant)
IT 50-02-2, Dexamethasone 50-07-7, Mitomycin C 50-18-0, Cyclophosphamide 50-35-1, Synovir 50-44-2, Mercaptopurine 50-69-1, Ribose 50-76-0, Dactinomycin 52-24-4, Thiotepa 53-03-2, Prednisone 55-86-7, Mechlorethamine hydrochloride 56-40-6, Glycine, biological studies 57-11-4, Stearic acid, biological studies 57-48-7, Fructose, biological studies 57-50-1, Sucrose, biological studies 57-88-5, Cholesterol, biological studies 59-23-4, Galactose, biological studies 61-90-5, Leucine, biological studies 63-42-3, Lactose 67-68-5, Sclerosol, biological studies 69-65-8, Mannitol 69-79-4, Maltose 70-00-8, Trifluridine 77-92-9, Citric acid, biological studies 79-41-4, biological studies 106-60-5, Aminolevulinic acid 112-92-5, Stearyl alcohol 127-07-1, Hydrea 134-62-3, OFF 143-67-9, Vinblastine sulfate 144-55-8, Sodium bicarbonate, biological studies 147-81-9, Arabinose 148-82-3, Alkeran 151-21-3, Sodium lauryl sulphate, biological studies 154-42-7, Tabloid 154-93-8, Carmustine 305-03-3, Ambochlorin 320-67-2, Azacitidine 366-70-1, Procarbazine hydrochloride 555-44-2, Glyceryl tripalmitate 557-04-0, Magnesium stearate 585-88-6, Maltitol 595-33-5, Megestrol acetate 1323-83-7, Glyceryl distearate 1327-43-1, Aluminum Magnesium silicon oxide 1327-53-3, Arsenic Trioxide 1492-18-8, Leucovorin calcium 2068-78-2, Vincristine sulfate 2068-78-2D, Vincristine sulfate, liposomes 2353-33-5, Dacogen 2921-88-2, Cyfos 3543-75-7, Treanda 4105-38-8, Uridine triacetate 4342-03-4, Dacarbazine 7447-40-7, Potassium chloride, biological studies 7447-41-8, Lithium chloride, biological studies 7487-88-9, Magnesium sulphate, biological studies 7631-86-9, Silica, biological studies 7647-14-5, Sodium chloride, biological studies 7757-82-6, Sodium sulphate, biological studies 7778-80-5, Potassium sulphate, biological studies 7786-30-3, Magnesium chloride, biological studies 9000-30-0, Guar gum 9000-69-5, Pectin 9000-92-4, Amylase 9003-39-8, Polyvinylpyrrolidone 9004-32-4, Carboxymethylcellulose 9004-34-6, Cellulose, biological studies 9004-34-6D, Cellulose, ethers 9004-35-7 9004-38-0, Cellulose acetate phthalate 9004-57-3, Ethyl cellulose 9004-62-0, Hydroxyethylcellulose 9004-64-2, Hydroxypropylcellulose 9004-65-3, Hydroxypropylmethylcellulose 9004-67-5, Methylcellulose 9005-25-8, Starch, biological studies 9005-32-7, Alginic acid 9005-38-3, Sodium alginate 9032-42-2, Hydroxyethyl-methylcellulose 9050-04-8 9050-31-1, Hydroxypropylmethylcellulose phthalate 9063-38-1, Sodium starch glycolate 10377-48-7, Lithium sulphate 11056-06-7, Bleomycin 11138-66-2, Xanthan gum 13010-47-4, Lomustine 13311-84-7, Flutamide 14807-96-6, Talc, biological studies 18641-57-1 19171-19-8, Pomalidomide 19767-45-4, Mesna 20830-81-3, Rubidomycin 23214-92-8, Doxil 24584-09-6, Totect 25086-15-1, Methacrylic acid-methyl methacrylate co-polymer 25212-88-8, Methacrylic acid-ethyl acrylate copolymer 25316-40-9, Doxorubicin hydrochloride 25322-68-3, Polyethylene glycol 26100-51-6, Polylactic acid 26124-68-5, Polyglycolic acid 26833-87-4, Omacetaxine mepesuccinate 31566-31-1, Glyceryl monostearate 33419-42-0, Etoposide 37380-42-0, Amberlite XAD

4 37380-43-1, Amberlite XAD 7 41575-94-4, Carboplatin 50935-57-4, Methyl vinyl ether-maleic acid copolymer ethyl ester 53237-50-6 54182-62-6, Polacrilin potassium 54578-91-5, Methyl vinyl ether-maleic acid copolymer butyl ester 56038-13-2, Sucralose 56390-09-1, Ellence 57248-88-1, Aredia 57852-57-0, Idamycin 61825-94-3, Eloxatin 64519-82-0, Isomalt 70476-82-3, Mitoxantrone hydrochloride 70535-77-2, Hydroxypropylmethylcellulose acetate succinate 74381-53-6, Leuprolide acetate 74811-65-7, Croscarmellose sodium 75607-67-9, Fludara 82640-04-8, Evista 83712-60-1, Defibrotide Sodium 84449-90-1, Keoxifene 85622-93-1, Methazolastone 89778-26-7, Fareston 90357-06-5, Bicalutamide 95058-81-4, Gemcitabine 97682-44-5, Irinotecan 98530-12-2, Interferon Alfa-2b 99011-02-6, Aldara 99614-01-4, Ondansetron hydrochloride 100286-90-6, Camptosar 100286-90-6D, Irinotecan hydrochloride, liposomes 104219-63-8, Amberlite XAD 16 108736-35-2, Somatuline Depot 110942-02-4, Aldesleukin 112809-51-5, Femara 114899-77-3, Trabectedin 114977-28-5, Docetaxel 117091-64-2, Etopophos 118072-93-8, Zoledronic acid 119413-54-6, Hycamtin 120511-73-1, Anastrozole 121181-53-1, Filgrastim 122111-03-9, Gemcitabine hydrochloride 122312-54-3 123119-31-3 123318-82-1, Clofarabine 125317-39-7, Navelbine 127984-74-1, Lanreotide acetate 128517-07-7, Istodax 129453-61-8, Faslodex 130167-69-0, Oncaspar 134774-45-1, Elitek 135729-62-3, Palonosetron hydrochloride 145781-92-6, Goserelin acetate 146464-95-1, Folotyn 148618-33-1, Ambersorb 572 148879-45-2, Ambersorb 563 149003-01-0, Dexrazoxane hydrochloride 149647-78-9, Vorinostat 150399-23-8, Alimta 153559-49-0, Bexarotene 154229-18-2, Abiraterone Acetate 154361-50-9, Capecitabine 159351-69-6, Everolimus 162394-19-6, Kepivance 162635-04-3, Temsirolimus 170729-80-3, Aprepitant 173146-27-5, Denileukin Diftitox 179324-69-7, Bortezomib 180288-69-1, Herceptin 183133-96-2, Cabazitaxel 183204-72-0, Tipiracil hydrochloride 183319-69-9, Erlotinib hydrochloride 184475-35-2, Gefitinib 191732-72-6, Lenalidomide 192391-48-3, Bexxar 205923-56-4, Cetuximab 206181-63-7, Ibritumomab Tiuxetan 208921-02-2, Tositumomab 208921-02-2D, Tositumomab, Iodine I-131 214766-78-6, Degarelix 215647-85-1, Peginterferon Alfa-2b 216503-57-0, Alemtuzumab 216974-75-3, Avastin 219989-84-1, Ixabepilone 220127-57-1, Gleevec 220578-59-6, Gemtuzumab 290297-26-6, Akynzeo 302962-49-8, Dasatinib 319460-85-0, Axitinib 339177-26-3, Panitumumab 341031-54-7, Sunitinib malate 380610-27-5, Perjeta 380843-75-4, Bosulif 388082-77-7, Lapatinib ditosylate 400046-53-9, Ozogamicin 404950-80-7, Farydak 417716-92-8, Lenvima 441045-17-6, Eribulin mesylate 443913-73-3, Vandetanib 477202-00-9, Ipilimumab 496775-62-3, Eltrombopag Olamine 541502-14-1, Siltuximab 571190-30-2, Ibrance 615258-40-7, Denosumab 635702-64-6, Pazopanib hydrochloride 641571-10-0, Nilotinib 679818-59-8, Arzerra 733030-01-8, Lonsurf 755037-03-7, Regorafenib 763113-22-0, Lynparza 843613-19-4, Ambersorb 348F 849217-68-1, Cabometyx 850140-72-6, Gilotrif 850140-73-7, Afatinib dimaleate 853426-35-4, Blinatumomab 857890-39-2, Lenvatinib mesylate 858102-79-1, Rolapitant hydrochloride 866323-14-0, Beleodaq 868540-17-4, Carfilzomib 870281-82-6, Idelalisib 871700-17-3, Mekinist 877399-52-5, Crizotinib 879085-55-9, Erivedge 906805-06-9, Necitumumab 910046-32-1, Gardasil 912337-47-4, Cervarix 914088-09-8, Adcetris 915087-33-1, Enzalutamide 915296-00-3, Elotuzumab 917381-47-6, Provenge 918504-65-1, Vemurafenib 930113-49-8, CAPOX
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(novel formulations of aprepitant)

IT 170729-80-3, Aprepitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(novel formulations of aprepitant)

RN 170729-80-3 CAPLUS

CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
WO 2018115888 A1	WO 2017-GB53864	Register|Global Dossier

L4 ANSWER 24 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2017:1728289 CAPLUS Full-text
DOCUMENT NUMBER: 168:9512
TITLE: Nanocrystal composition for improving oral absorption of insoluble drug
INVENTOR(S): Liu, Yan; Li, Xueping; Li, Xinru; Zhou, Yanxia
PATENT ASSIGNEE(S): Peking University, Peop. Rep. China
SOURCE: Faming Zhuanli Shenqing, 11pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

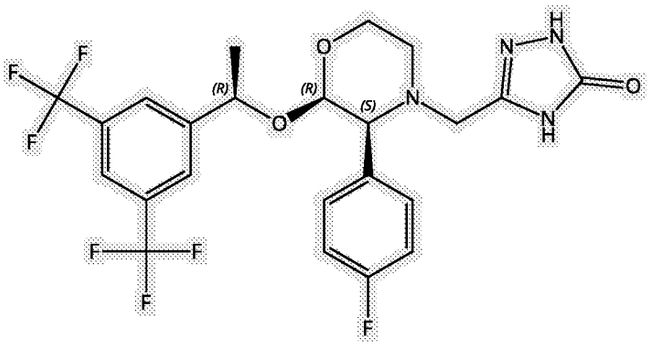
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 107303272	A	20171031	CN 2016-10239333	20160418

PRIORITY APPLN. INFO.: CN 2016-10239333 20160418
PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
CN 107303272	A	Dead	20220527

OTHER SOURCE(S): CASFORMULTNS 2017:1728289
AB The title compn. is composed of an insol. drug, a stabilizer, the ligand of the specific receptor expressed by intestinal epithelial cell and/or substrate of transporter and optional pharmaceutically acceptable auxiliary, and is prepd. by prepg. into a suspension and lyophilizing. The expt. proves that the compn. can remarkably improve the oral absorption of the insol. drug so as to provide the prepn. strategy for insol. drug oral administration.
IPCI A61K0009-10; A61K0009-19; A61K0047-10; A61K0047-42; A61K0047-22; A61K0047-26; A61K0047-18; A61K0047-24; A61K0047-38; A61K0047-32; A61K0031-4745; A61K0031-337; A61K0031-7048; A61K0031-436; A61K0031-5377; A61K0031-357
IPCR A61K0009-10 [I]; A61K0009-19 [I]; A61K0031-337 [I]; A61K0031-357 [I]; A61K0031-436 [I]; A61K0031-4745 [I]; A61K0031-5377 [I]; A61K0031-7048 [I]; A61K0047-10 [I]; A61K0047-18 [I]; A61K0047-22 [I]; A61K0047-24 [I]; A61K0047-26 [I]; A61K0047-32 [I]; A61K0047-38 [I]; A61K0047-42 [I]
CC 63-6 (Pharmaceuticals)
IT Amino acids
Dipeptides
Ethoxylated hydrogenated castor oil
Lecithins
Polyoxyalkylenes
Soya phospholipids
Transferrins

Tripeptides
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nanocrystal compn. for improving oral absorption of insol. drug)
IT 50-02-2, Dexamethasone 50-04-4, Cortisone acetate 426-13-1, Fluorometholone 458-37-7, Curcumin 15687-27-1, Ibuprofen 19685-09-7, 10-Hydroxycamptothecin 22888-70-6, Silibinin 25316-40-9, Adriamycin 29767-20-2, Teniposide 33069-62-4, Paclitaxel 33419-42-0, Etoposide 34368-04-2, Dobutamine 35354-74-6, Honokiol 49562-28-9, Fenofibrate 51333-22-3, Budesonide 59865-13-3, Cyclosporin A 65666-07-1, Silymarin 80474-14-2, Fluticasone propionate 84625-61-6, Itraconazole 91421-42-0, 9-Nitrocamptothecin 104987-11-3, Tacrolimus 114977-28-5, Docetaxel 170729-80-3, Aprepitant
RL: NANO (Nanomaterial); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nanocrystal compn. for improving oral absorption of insol. drug)
IT 170729-80-3, Aprepitant
RL: NANO (Nanomaterial); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nanocrystal compn. for improving oral absorption of insol. drug)
RN 170729-80-3 CAPLUS
CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
CN 107303272 A	CN 2016-10239333	Register|Global Dossier

L4 ANSWER 25 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2017:1554024 CAPLUS Full-text
DOCUMENT NUMBER: 168:18112
TITLE: Biorelevant Drug Solubility Enhancement Modeled by a Linear Solvation Energy Relationship
AUTHOR(S): Niederquell, Andreas; Kuentz, Martin
CORPORATE SOURCE: Institute of Pharma Technology, University of Applied Sciences and Arts Northwestern Switzerland, Muttenz, 4132, Switz.
SOURCE: Journal of Pharmaceutical Sciences (Philadelphia, PA, United States) (2018), 107(1), 503-506
CODEN: JPMSAE; ISSN: 0022-3549
DIGITAL OBJECT ID: 10.1016/j.xphs.2017.08.017
PUBLISHER: Elsevier Inc.
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
AB It is for the pharmaceutical sciences of vital importance to understand how drugs are solubilized in biorelevant media. However, the complexity

of fasted state simulated intestinal fluid (FaSSIF) has so far hampered adequate soly. modeling. The present study focuses on apparently neutral compds. at physiol. pH and a linear free energy relationship is introduced for biorelevant drug solubilization. Based on literature data of 40 compds., the Abraham solvation descriptors were calcd. from chem. structure to then predict the ratio of soly. enhancement log(SE) in FaSSIF compared to aq. buffer soly. at pH 6.5. A suitable model was obtained with R2 of 0.810 and notable were esp. the pos. effect of McGowan's characteristic vol. and the neg. effect of drug basicity. A neg. influence on log(SE) was further evidenced for dipolarity/polarizability and for the excess molar refraction descriptor. A pos. solubilization effect was obtained for drug acidity and hence the tendency for proton donation, which was likely due to the different proton-accepting moieties of taurocholic acid and lecithin that are both present in the mixed colloids of FaSSIF. Overall, an improved understanding was achieved regarding the mol. features that are driving drug solubilization in biorelevant media.

CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1

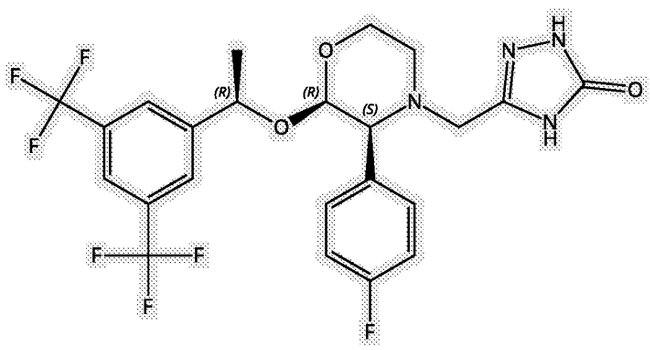
IT Lecithins
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(biorelevant drug soly. enhancement modeled by a linear solvation energy relationship)

IT 50-02-2, Dexamethasone 50-28-2, Estra-1,3,5(10)-triene-3,17-diol (17β)-, biological studies 52-01-7, Spironolactone 53-03-2, Prednisone 53-16-7, Estrone, biological studies 57-41-0, Phenytoin 57-83-0, Progesterone, biological studies 58-22-0, Testosterone 58-32-2, Dipyridamole 58-94-6, Chlorothiazide 81-24-3, Taurocholic acid 81-81-2, Warfarin 84-17-3, Dienestrol 126-07-8, Griseofulvin 298-46-4, Carbamazepine 439-14-5, Diazepam 846-49-1, Lorazepam 17230-88-5 23288-49-5, Probucol 39562-70-4, Nitrendipine 49562-28-9, Fenofibrate 51803-78-2, Nimesulide 54965-21-8, Albendazole 55268-74-1 59865-13-3, Cyclosporine 65646-68-6, Fenretinide 70288-86-7, Ivermectin 72509-76-3 73963-72-1, Cilostazole 75330-75-5, Lovastatin 95233-18-4, Atovaquone 103577-45-3, Lansoprazole 124423-84-3, Panadiplon 138402-11-6 154598-52-4 161814-49-9, Amprenavir 162011-90-7, Rofecoxib 169590-42-5, Celecoxib 170729-80-3, Aprepitant 192725-17-0, Lopinavir 262352-17-0, Torcetrapib
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(biorelevant drug soly. enhancement modeled by a linear solvation energy relationship)

IT 170729-80-3, Aprepitant
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(biorelevant drug soly. enhancement modeled by a linear solvation energy relationship)

RN 170729-80-3 CAPLUS

CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)

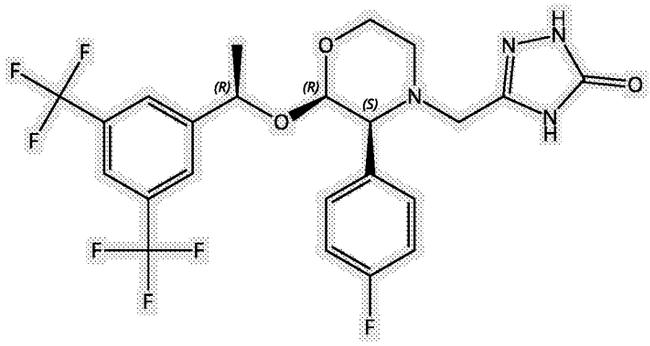


Absolute stereochemistry shown
Rotation (+)

OS.CITING REF COUNT: 18 THERE ARE 18 CAPLUS RECORDS THAT CITE THIS RECORD (18 CITINGS)
REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 26 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2017:1232902 CAPLUS Full-text
DOCUMENT NUMBER: 167:591636
TITLE: Influence of Physiological Gastrointestinal Surfactant Ratio on the Equilibrium Solubility of BCS Class II Drugs Investigated Using a Four Component Mixture Design
AUTHOR(S): Zhou, Zhou; Dunn, Claire; Khadra, Ibrahim; Wilson, Clive G.; Halbert, Gavin W.
CORPORATE SOURCE: Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow, G4 0RE, UK
SOURCE: Molecular Pharmaceutics (2017), 14(12), 4132-4144
CODEN: MPOHBP; ISSN: 1543-8384
DIGITAL OBJECT ID: 10.1021/acs.molpharmaceut.7b00354
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
AB The absorption of poorly water-sol. drugs is influenced by the luminal gastrointestinal fluid content and compn. which controls soly. Simulated intestinal fluids have been introduced into dissoln. testing including endogenous amphiphiles and digested lipids at physiol. levels; however, in vivo individual variation exists in the concns. of these components, which will alter drug absorption through an effect on soly. The use of a factorial design of expt. and varying media by introducing different levels of bile, lecithin and digested lipids has been previously reported, but here we investigate the soly. variation of poorly-sol. drugs through more complex biorelevant amphiphile interactions. A four component mixt. design was conducted to understand the solubilization capacity and interactions of bile salt, lecithin, oleate and monoglyceride with a const. total concn. (11.7 mM) but varying molar ratios. The equil. soly. of seven low soly. acidic (zafirlukast), basic (aprepitant, carvedilol) and neutral (fenofibrate, felodipine, griseofulvin and spironolactone) drugs was investigated. Soly. results are comparable with literature values and also our own previously published design of expt. studies. Results indicate that solubilization is not a sum accumulation of individual amphiphile concns., but a drug specific effect through interactions of mixed amphiphile compns. with the drug. This is probably due to a combined interaction of drug characteristics for example lipophilicity, mol. shape and ionization with amphiphile components, which can generate specific drug-micelle affinities. The proportion of each component can have a remarkable influence on soly. with in some cases the highest and lowest points close to each other. A single point soly. measurement in a fixed compn. simulated media or human intestinal fluid sample will therefore provide a value without knowledge of the surrounding soly. topog. meaning that variability may be overlooked. This study has demonstrated how the amphiphile ratios influence drug soly. and highlights the importance of the envelope of physiol. variation when simulating in vivo drug behavior.
CC 63-6 (Pharmaceuticals)
IT 52-01-7, Spironolactone 126-07-8, Griseofulvin 49562-28-9, Fenofibrate 72509-76-3, Felodipine 72956-09-3, Carvedilol 107753-78-6, Zafirlukast 170729-80-3, Aprepitant
RL: PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(influence of physiol. gastrointestinal surfactant ratio on equil. soly. of BCS class II drugs investigated using a four component mixt. design)
IT 170729-80-3, Aprepitant
RL: PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(influence of physiol. gastrointestinal surfactant ratio on equil. soly. of BCS class II drugs investigated using a four component mixt. design)
RN 170729-80-3 CAPLUS
CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX

NAME)



Absolute stereochemistry shown
Rotation (+)

OS.CITING REF COUNT: 28 THERE ARE 28 CAPLUS RECORDS THAT CITE THIS RECORD (28 CITINGS)
REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 27 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2016:2157637 CAPLUS Full-text
DOCUMENT NUMBER: 166:118691
TITLE: Cosmeceutical compositions comprising polyalkylene glycols
INVENTOR(S): Schmaus, Gerhard; Lange, Sabine
PATENT ASSIGNEE(S): Symrise AG, Germany
ULTIMATE OWNER: SYMRISE AG
ULTIMATE OWNER STANDARD: Symrise
SOURCE: PCT Int. Appl., 56pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2016207084	A1	20161229	WO 2016-EP64109	20160619
EP 3108941	A1	20161228	EP 2015-173373	20150623
EP 3108941	B1	20180509		
KR 2018015265	A	20180212	KR 2018-7002058	20160619
KR 2117171	B1	20200601		
MX 2017016226	A	20180223	MX 2017-16226	20160619
CN 107847772	A	20180327	CN 2016-80045857	20160619
CN 107847772	B	20220104		
JP 2018518496	T	20180712	JP 2017-565942	20160619
JP 6945458	B2	20211006		
BR 112017027546	A2	20180821	BR 2017-112017027546	20160619
BR 112017027546	B1	20220426		
IN 201717044256	A	20180105	IN 2017-17044256	20171208
US 20180185301	A1	20180705	US 2017-15736494	20171214

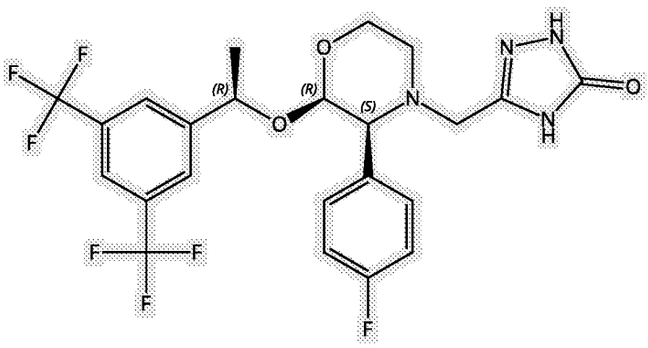
PRIORITY APPLN. INFO.:
EP 2015-173373 A 20150623
WO 2016-EP64109 W 20160619

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
WO 2016207084	A1	Dead	20201201
EP 3108941	A1	Indeterminate	20201106
EP 3108941	B1	Indeterminate	20201107
KR 2018015265	A	Alive	20201121
KR 2117171	B1	Alive	20201121
MX 2017016226	A	Alive	20201121
CN 107847772	A	Alive	20201121
CN 107847772	B	Alive	20220120

JP 2018518496 T Alive 20201120
JP 6945458 B2 Alive 20211118
BR 112017027546 A2 Alive 20220519
BR 112017027546 B1 Alive 20220519
US 20180185301 A1 Dead 20220818
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASFORMULTNS 2016:2157637
AB Suggested are compns. comprising or consisting of specific polyalkylene glycol deriv. as pharmaceutical actives for preventing, treating and/or curing itchy conditions of human skin and scalp, and/or providing a PAR-2 antagonistic effect to human skin and scalp.
IPCI A61Q0019-00 [I]; A61Q0005-00 [I]; A61Q0005-12 [I]; A61Q0017-04 [I]; A61Q0019-02 [I]; A61Q0015-00 [I]; A61K0008-39 [I]; A61K0008-33 [I]; A61K0031-08 [I]; A61K0031-25 [I]; A61P0017-04 [I]
IPCR A61K0008-33 [I]; A61Q0019-00 [I]; A61K0008-39 [I]; A61K0031-08 [I]; A61K0031-25 [I]; A61P0017-04 [I]; A61Q0005-00 [I]; A61Q0005-12 [I]; A61Q0015-00 [I]; A61Q0017-04 [I]; A61Q0019-02 [I]
CC 62-4 (Essential Oils and Cosmetics)
Section cross-reference(s): 63
IT Amino acids
Cannabinoids
Carbohydrates
Ceramides
Collagens
Corticosteroids
Disaccharides
Elastins
Glycosphingolipids
Hydroxy fatty acids
Hydroxycarboxylic acids
Lanolin
Lecithins
Oligosaccharides
Petrolatum
Phytosterols
Polyoxyalkylenes
Pyrazoles
Steroids
Tocopherols
RL: COS (Cosmetic use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cosmeceutical compns. comprising polyalkylene glycols)
IT 50-02-2 50-21-5, biological studies 50-23-7 50-33-9, biological studies 50-78-2 50-99-7, D-Glucose, biological studies 53-06-5 53-86-1 56-81-5, 1,2,3-Propanetriol, biological studies 57-13-6, Urea, biological studies 57-48-7, D-Fructose, biological studies 57-55-6, 1,2-Propanediol, biological studies 57-88-5, Cholest-5-en-3-ol (3β)-, biological studies 58-95-7 59-23-4, D-Galactose, biological studies 61-68-7 63-42-3 69-46-5 72-17-3 77-52-1 77-92-9, biological studies 81-13-0 83-43-2 89-78-1 89-79-2 97-59-6 98-52-2 104-98-3 124-04-9D, Hexanedioic acid, acyl derivs. 129-20-4 312-93-6 472-15-1 502-65-8, ψ,ψ-Carotene 515-69-5 520-36-5 530-78-9 544-31-0 552-94-3 555-66-8 578-74-5 644-62-2 873-94-9 1117-77-7 1117-86-8, 1,2-Octanediol 1405-86-3, Glycyrrhizin 1406-18-4, Vitamin E 2304-80-5 3458-28-4, D-Mannose 3804-01-1 4394-00-7 5343-92-0, 1,2-Pentanediol 6915-15-7 6920-22-5, 1,2-Hexanediol 9004-61-9, Hyaluronic acid 9007-28-7 9012-76-4, Chitosan 9041-22-9, β-D-Glucan 13539-59-8 13609-67-1 15307-86-5 15687-27-1 22204-53-1 24938-91-8 26171-23-3 27113-22-0 30748-29-9 34645-84-6 36322-90-4 36945-98-9 38194-50-2 41736-92-9 51115-67-4 51234-28-7 53254-77-6 53597-27-6 55965-23-6 58253-27-3, Gingerol 58749-22-7 59804-37-4 59870-68-7 61723-78-2 63187-91-7 74563-64-7 77341-67-4 106729-72-0 108766-16-1 110483-07-3 170729-80-3 185740-18-5 185915-25-7 189128-20-9 207792-35-6 211184-47-3 220621-22-7 381224-15-3 506412-91-5 521981-60-2 637336-79-9 697235-49-7 857557-19-8 1122460-01-8
RL: COS (Cosmetic use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cosmeceutical compns. comprising polyalkylene glycols)
IT 170729-80-3
RL: COS (Cosmetic use); THU (Therapeutic use); BIOL (Biological study);

USES (Uses)
(cosmeceutical compns. comprising polyalkylene glycols)
RN 170729-80-3 CAPLUS
CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
BR 112017027546 A2	BR 2017-112017027546	Register
BR 112017027546 B1	BR 2017-112017027546	Register
CN 107847772 A	CN 2016-80045857	Register|Global Dossier
CN 107847772 B	CN 2016-80045857	Register|Global Dossier
EP 3108941 A1	EP 2015-173373	Register|Federated Reg.
EP 3108941 B1	EP 2015-173373	Register|Federated Reg.
IN 201717044256 A	IN 2017-17044256	Register
JP 2018518496 T	JP 2017-565942	Register|Global Dossier
JP 6945458 B2	JP 2017-565942	Register|Global Dossier
KR 2018015265 A	KR 2018-7002058	Register|Global Dossier
KR 2117171 B1	KR 2018-7002058	Register|Global Dossier
MX 2017016226 A	MX 2017-16226	Register
US 20180185301 A1	US 2017-15736494	Register|Global Dossier
WO 2016207084 A1	WO 2016-EP64109	Register|Global Dossier

L4 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2016:2152998 CAPLUS Full-text
DOCUMENT NUMBER: 166:112176
TITLE: Cosmeceutical compositions comprising polyalkylene glycols
INVENTOR(S): Schmaus, Gerhard; Lange, Sabine
PATENT ASSIGNEE(S): Symrise AG, Germany
ULTIMATE OWNER: SYMRISE AG
ULTIMATE OWNER STANDARD: Symrise
SOURCE: Eur. Pat. Appl., 46pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 3108941	A1	20161228	EP 2015-173373	20150623
EP 3108941	B1	20180509		
WO 2016207084	A1	20161229	WO 2016-EP64109	20160619
KR 2018015265	A	20180212	KR 2018-7002058	20160619
KR 2117171	B1	20200601		
MX 2017016226	A	20180223	MX 2017-16226	20160619

CN 107847772	A	20180327	CN 2016-80045857		20160619
CN 107847772	B	20220104			
JP 2018518496	T	20180712	JP 2017-565942		20160619
JP 6945458	B2	20211006			
BR 112017027546	A2	20180821	BR 2017-112017027546		20160619
BR 112017027546	B1	20220426			
IN 201717044256	A	20180105	IN 2017-17044256		20171208
US 20180185301	A1	20180705	US 2017-15736494		20171214
PRIORITY APPLN. INFO.:			EP 2015-173373	A	20150623
			WO 2016-EP64109	W	20160619

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
EP 3108941	A1	Indeterminate	20201106
EP 3108941	B1	Indeterminate	20201107
WO 2016207084	A1	Dead	20201201
KR 2018015265	A	Alive	20201121
KR 2117171	B1	Alive	20201121
MX 2017016226	A	Alive	20201121
CN 107847772	A	Alive	20201121
CN 107847772	B	Alive	20220120
JP 2018518496	T	Alive	20201120
JP 6945458	B2	Alive	20211118
BR 112017027546	A2	Alive	20220519
BR 112017027546	B1	Alive	20220519
US 20180185301	A1	Dead	20220818

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OTHER SOURCE(S): CASFORMULTNS 2016:2152998

AB Suggested are compns. comprising or consisting of specific polyalkylene glycol deriv. as pharmaceutical actives for preventing, treating and/or curing itchy conditions of human skin and scalp, and/or providing a PAR-2 antagonistic effect to human skin and scalp.

IPCI A61Q0019-00 [I]; A61Q0005-00 [I]; A61Q0005-12 [I]; A61Q0017-04 [I]; A61Q0019-02 [I]; A61Q0015-00 [I]; A61K0008-39 [I]; A61K0008-33 [I]; A61K0031-08 [I]; A61K0031-25 [I]; A61P0017-04 [I]

IPCR A61Q0019-00 [I]; A61K0008-33 [I]; A61K0008-39 [I]; A61K0031-08 [I]; A61K0031-25 [I]; A61P0017-04 [I]; A61Q0005-00 [I]; A61Q0005-12 [I]; A61Q0015-00 [I]; A61Q0017-04 [I]; A61Q0019-02 [I]

CC 62-4 (Essential Oils and Cosmetics)
Section cross-reference(s): 63

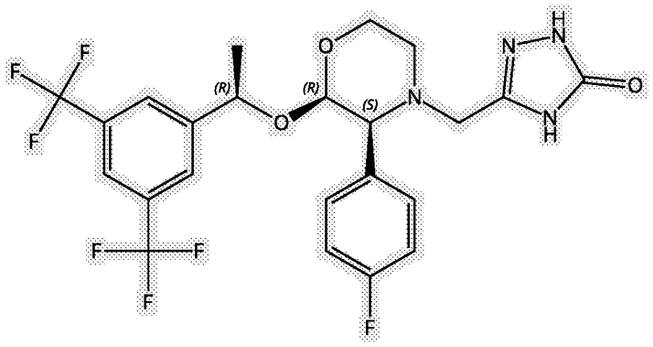
IT Amino acids
Cannabinoids
Carbohydrates
Ceramides
Collagens
Corticosteroids
Disaccharides
Elastins
Glycosphingolipids
Hydroxy fatty acids
Hydroxycarboxylic acids
Lanolin
Lecithins
Oligosaccharides
Petrolatum
Phytosterols
Polyoxyalkylenes
Pyrazoles
Steroids
Tocopherols
RL: COS (Cosmetic use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cosmeceutical compns. comprising polyalkylene glycols)

IT 50-02-2, Dexamethasone 50-21-5, Lactic acid, biological studies 50-23-7, Hydrocortisone 50-33-9, Phenylbutazone, biological studies 50-78-2, Aspirin 50-99-7, D-Glucose, biological studies 53-06-5, Cortisone 53-86-1, Indomethacin 56-81-5, Glycerol, biological studies 57-13-6, Urea, biological studies 57-48-7, D-Fructose, biological studies 57-55-6, Propylene glycol, biological studies 57-88-5, Cholesterol, biological studies 58-95-7, Tocopheryl acetate 59-23-4, D-Galactose, biological studies 61-68-7, Mefenamic acid 63-42-3, Lactose 69-46-5, Solprin 72-17-3, Sodium lactate 77-52-1, Ursolic

acid 77-92-9, Citric acid, biological studies 81-13-0 83-43-2,
Methylprednisolone 89-78-1, Menthol 89-79-2 97-59-6 98-52-2
104-98-3 124-04-9D, Adipic acid, acyl derivs. 129-20-4,
Oxyphenylbutazone 312-93-6, Dexamethasone phosphate 472-15-1, Betulic
acid 502-65-8, ψ,ψ-Carotene 515-69-5, α-Bisabolol
520-36-5, Apigenin 530-78-9, Flufenamic acid 544-31-0, N-Palmitoyl
Ethanolamine 552-94-3, Disalcid 555-66-8 578-74-5 629-54-9,
Hexadecanamide 644-62-2, Meclofenamic acid 873-94-9 1117-77-7
1117-86-8, 1,2-Octanediol 1405-86-3, Glycyrrhizin 1406-18-4, Vitamin E
2304-80-5 3458-28-4, D-Mannose 3804-01-1 4394-00-7, Niflumic acid
5343-92-0, 1,2-Pentanediol 6915-15-7, Malic acid 6920-22-5,
1,2-Hexanediol 9004-61-9, Hyaluronic acid 9007-28-7, Chondroitin
sulfate 9012-76-4, Chitosan 9041-22-9, β-Glucan 13539-59-8
13609-67-1, Hydrocortisone 17-butyrate 15307-86-5, Diclofenac
15687-27-1, Ibuprofen 22204-53-1, Naproxen 24938-91-8, Polyethylene
glycol Tridecyl ether 26171-23-3, Tolmetin 27113-22-0 30748-29-9,
Feprazone 34645-84-6, Fenclofenac 36322-90-4, Piroxicam 36945-98-9,
Icilin 38194-50-2, Sulindac 41736-92-9 51115-67-4,
2-Isopropyl-N-2,3-trimethylbutanamide 51234-28-7, Benoxaprofen
53254-77-6 53597-27-6, Fendosal 55965-23-6 58253-27-3, Gingerol
58749-22-7 59804-37-4, Tenoxicam 59870-68-7 61723-78-2 63187-91-7
74563-64-7 77341-67-4 106729-72-0 108766-16-1 170729-80-3
185740-18-5 185915-25-7, L-Menthyl lactate 189128-20-9 207792-35-6,
3-Menthoxypropane-1,2-diol 211184-47-3 220621-22-7 381224-15-3
506412-91-5 521981-60-2 637336-79-9 697235-49-7 857557-19-8
1122460-01-8
RL: COS (Cosmetic use); THU (Therapeutic use); BIOL (Biological study);
USES (Uses)
(cosmeceutical compns. comprising polyalkylene glycols)

IT 170729-80-3
RL: COS (Cosmetic use); THU (Therapeutic use); BIOL (Biological study);
USES (Uses)
(cosmeceutical compns. comprising polyalkylene glycols)

RN 170729-80-3 CAPLUS
CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phen
yl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX
NAME)



Absolute stereochemistry shown
Rotation (+)

OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD
(1 CITINGS)
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
BR 112017027546 A2	BR 2017-112017027546	Register
BR 112017027546 B1	BR 2017-112017027546	Register
CN 107847772 A	CN 2016-80045857	Register|Global Dossier
CN 107847772 B	CN 2016-80045857	Register|Global Dossier
EP 3108941 A1	EP 2015-173373	Register|Federated Reg.

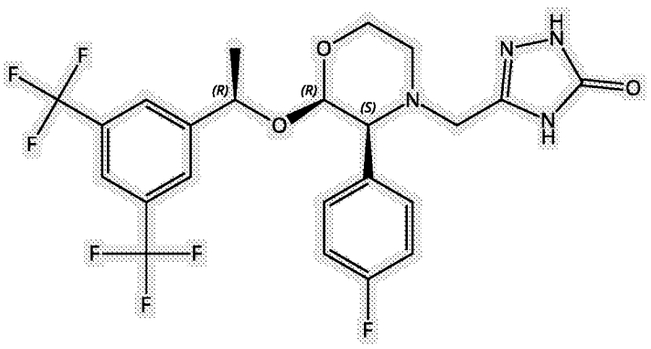
EP 3108941 B1	EP 2015-173373	Register|Federated Reg.
IN 201717044256 A	IN 2017-17044256	Register
JP 2018518496 T	JP 2017-565942	Register|Global Dossier
JP 6945458 B2	JP 2017-565942	Register|Global Dossier
KR 2018015265 A	KR 2018-7002058	Register|Global Dossier
KR 2117171 B1	KR 2018-7002058	Register|Global Dossier
MX 2017016226 A	MX 2017-16226	Register
US 20180185301 A1	US 2017-15736494	Register|Global Dossier
WO 2016207084 A1	WO 2016-EP64109	Register|Global Dossier

L4 ANSWER 29 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2016:2116494 CAPLUS Full-text
DOCUMENT NUMBER: 172:545657
TITLE: Statistical investigation of simulated fed intestinal media composition on the equilibrium solubility of oral drugs
AUTHOR(S): Zhou, Zhou; Dunn, Claire; Khadra, Ibrahim; Wilson, Clive G.; Halbert, Gavin W.
CORPORATE SOURCE: Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow, G4 0RE, UK
SOURCE: European Journal of Pharmaceutical Sciences (2017), 99, 95-104
CODEN: EPSCED; ISSN: 0928-0987
DIGITAL OBJECT ID: 10.1016/j.ejps.2016.12.008
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English

AB Gastrointestinal fluid is a complex milieu and it is recognized that gut drug soly. is different to that obsd. in simple aq. buffers. Simulated gastrointestinal media have been developed covering fasted and fed states to facilitate in vitro prediction of gut soly. and product dissoln. However, the combination of bile salts, phospholipids, fatty acids and proteins in an aq. buffered system creates multiple phases and drug soly. is therefore a complex interaction between these components, which may create unique environments for each API. The impact on soly. can be assessed through a statistical design of expt. (DoE) approach, to det. the influence and relationships between factors. In this paper DoE has been applied to fed simulated gastrointestinal media consisting of eight components (pH, bile salt, lecithin, sodium oleate, monoglyceride, buffer, salt and pancreatin) using a two level D-optimal design with forty-four duplicate measurements and four center points. The equil. soly. of a range of poorly sol. acidic (indomethacin, ibuprofen, phenytoin, valsartan, zafirlukast), basic (aprepitant, carvedilol, tadalafil, bromocriptine) and neutral (fenofibrate, felodipine, probucol, itraconazole) drugs was investigated. Results indicate that the DoE provides equil. soly. values that are comparable to literature results for other simulated fed gastrointestinal media systems or human intestinal fluid samples. For acidic drugs the influence of pH predominates but other significant factors related to oleate and bile salt or interactions between them are present. For basic drugs pH, oleate and bile salt have equal significance along with interactions between pH and oleate and lecithin and oleate. Neutral drugs show diverse effects of the media components particularly with regard to oleate, bile salt, pH and lecithin but the presence of monoglyceride, pancreatin and buffer have significant but smaller effects on soly. There are fourteen significant interactions between factors mainly related to the surfactant components and pH, indicating that the soly. of neutral drugs in fed simulated media is complex. The results also indicate that the equil. soly. of each drug can exhibit individualistic behavior assocd. with the drug's chem. structure, physicochem. properties and interaction with media components. The utility of DoE for fed simulated media has been demonstrated providing equil. soly. values comparable with similar in vitro systems while also providing greater information on the influence of media factors and their interactions. The detn. of a drug's gastrointestinal soly. envelope provides useful limits that can potentially be applied to in silico modeling and in vivo expts.

CC 63-5 (Pharmaceuticals)
IT 53-86-1, Indomethacin 57-41-0, Phenytoin 15687-27-1, Ibuprofen 23288-49-5, Probucol 25614-03-3, Bromocriptine 49562-28-9, Fenofibrate 72509-76-3, Felodipine 72956-09-3, Carvedilol 84625-61-6, Itraconazole 107753-78-6, Zafirlukast 137862-53-4, Valsartan 170729-80-3,

Aprepitant 171596-29-5, Tadalafil
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(statistical investigation of simulated fed intestinal media compn. effect on equil. soly. of oral drugs)
IT 170729-80-3, Aprepitant
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(statistical investigation of simulated fed intestinal media compn. effect on equil. soly. of oral drugs)
RN 170729-80-3 CAPLUS
CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

OS.CITING REF COUNT: 33 THERE ARE 33 CAPLUS RECORDS THAT CITE THIS RECORD (33 CITINGS)
REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

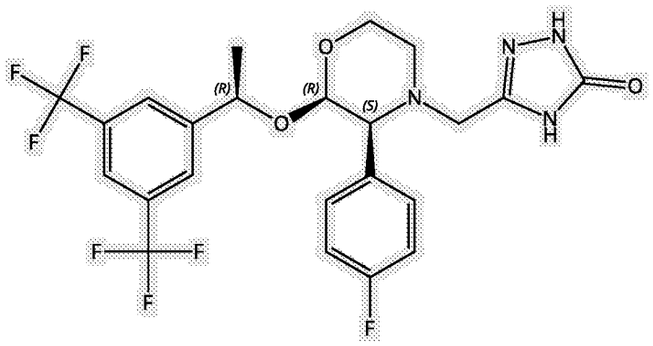
L4 ANSWER 30 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2016:2039523 CAPLUS Full-text
DOCUMENT NUMBER: 167:295158
TITLE: Stable injectable pharmaceutical composition of neurokinin 1 receptor antagonist and process for preparation thereof
INVENTOR(S): Karavas, Evangelos; Koutris, Efthimios; Bikiaris, Dimitrios; Chatidou, Sotiria; Diakidou, Amalia; Barmpalexis, Panagiotis; Konstanti, Louiza; Minioti, Katerina
PATENT ASSIGNEE(S): Pharmathen S.A., Greece
ULTIMATE OWNER: PARTNERS GROUP HOLDING AG
ULTIMATE OWNER STANDARD: Partners Group
SOURCE: U.S. Pat. Appl. Publ., No pp. given
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 20150165045	A1	20150618	US 2014-14412147		20141230
WO 2014005606	A1	20140109	WO 2012-EP2854		20120706
US 20200237920	A1	20200730	US 2020-16851779		20200417
PRIORITY APPLN. INFO.:			WO 2012-EP2854	W	20120706
			US 2014-14412147	A1	20141230

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
US 20150165045	A1	Dead	20220105
WO 2014005606	A1	Dead	20201202

US 20200237920 A1 Dead 20231109
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASFORMULTNS 2016:2039523
AB The present invention relates to a controlled release sterile injectable formulation in the form of soln., suspension or sol-gel formulation for i.m. or s.c. administration comprising a therapeutically effective amt. of a neurokinin 1 receptor antagonist, in particular Aprepitant or Fosaprepitant or pharmaceutical acceptable salt, deriv. or metabolite thereof. It also relates to a process for developing such formulations.
IPCI A61K0047-38 [I]; A61K0031-675 [I]; A61K0047-34 [I]; A61K0047-44 [I]; A61K0047-14 [I]; A61K0047-46 [I]; A61K0031-5377 [I]; A61K0009-00 [I]
IPCR A61K0047-38 [I]; A61K0009-00 [I]; A61K0031-5377 [I]; A61K0031-675 [I]; A61K0047-14 [I]; A61K0047-34 [I]; A61K0047-44 [I]; A61K0047-46 [I]
NCL 514/090.000; 514/230.800
CC 63-6 (Pharmaceuticals)
IT Castor oil
Cottonseed oil
Gelatins
Lecithins
Polymers
Polyoxyalkylenes
Sesame oil
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. of stable injectable pharmaceutical compns. of neurokinin 1 receptor antagonist)
IT 170729-80-3 172673-20-0 265121-04-8
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. of stable injectable pharmaceutical compns. of neurokinin 1 receptor antagonist)
IT 170729-80-3
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. of stable injectable pharmaceutical compns. of neurokinin 1 receptor antagonist)
RN 170729-80-3 CAPLUS
CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
US 20150165045 A1	US 2014-14412147	Register|Global Dossier
US 20200237920 A1	US 2020-16851779	Register|Global Dossier
WO 2014005606 A1	WO 2012-EP2854	Register|Global Dossier

L4 ANSWER 31 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2016:1859837 CAPLUS Full-text
DOCUMENT NUMBER: 166:232413

TITLE: Evaluation of Pentravan, Pentravan Plus, Phytobase, Lipovan and Pluronic Lecithin Organogel for the transdermal administration of antiemetic drugs to treat chemotherapy-induced nausea and vomiting at the hospital

AUTHOR(S): Bourdon, F.; Lecoeur, M.; Leconte, L.; Ultre, V.; Kouach, M.; Odou, P.; Vaccher, C.; Foulon, C.

CORPORATE SOURCE: EA GRITA-7365-Groupe de Recherche sur les formes Injectables et les Technologies Associees, Univ. Lille, Lille, F-59000, Fr.

SOURCE: International Journal of Pharmaceutics (Amsterdam, Netherlands) (2016), 515(1-2), 774-787
CODEN: IJPHDE; ISSN: 0378-5173

DIGITAL OBJECT ID: 10.1016/j.ijpharm.2016.11.014

PUBLISHER: Elsevier B.V.

DOCUMENT TYPE: Journal; (online computer file)

LANGUAGE: English

OTHER SOURCE(S): CASFORMULTNS 2016:1859837

AB The objective of this study was to evaluate five com. ready-to-use transdermal vehicles (Phytobase, Lipovan, Pentravan, Pentravan Plus and Pluronic Lecithin Organogel (PLO)), for the compounding of three antiemetic drugs (ondansetron, dexamethasone and aprepitant) and their administration in combination to treat chemotherapy-induced nausea and vomiting (CINV) at the hospital. Drugs were individually formulated in these vehicles and in mixt. in Pentravan Plus using different penetration enhancers. Quality control of the forms has demonstrated that formulation process was mastered and convenient for the hospital (time required: 20 min). Diffusion expts. through synthetic membranes and pig ear epidermis performed using Franz-type diffusion cells, have shown that the release and permeation process were greater for ondansetron than for dexamethasone and aprepitant, with a release step not limiting. As permeation of aprepitant was too low, it was discarded of the study. When ondansetron and dexamethasone were compounded in combination in Pentravan Plus, the most efficient vehicle, a permeation decrease was obsd. Finally, the use of tween 20 instead of EtOH as chem. enhancer has led to 2-fold factor increase in the flux of dexamethasone, resulting in fluxes convenient for transdermal administration of ondansetron to a child, but insufficient for an adult and for dexamethasone.

CC 63-6 (Pharmaceuticals)

ST antiemitic Pentravan Plus Phytobase Lipovan Pluronic Lecithin Organogel skin

IT Antiemetics
Biological permeation
Chemotherapy
Child
Combination chemotherapy
Drug delivery systems
Drug toxicity
Homo sapiens
Human
Nausea
Organogels
Permeation enhancers
Skin
Solubility
Transdermal drug delivery systems
Vomiting
(evaluation of Pentravan, Pentravan Plus, Phytobase, Lipovan and Pluronic Lecithin Organogel for the transdermal administration of antiemetic drugs to treat chemotherapy-induced nausea and vomiting at the hospital)

IT 1610779-74-2, Pentravan 1610779-77-5, Pluronic Lecithin Organogel 2074721-57-4, Pentravan Plus 2074721-58-5, Phytobase 2074721-59-6, Lipovan
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(evaluation of Pentravan, Pentravan Plus, Phytobase, Lipovan and Pluronic Lecithin Organogel for the transdermal administration of antiemetic drugs to treat chemotherapy-induced nausea and vomiting at the hospital)

IT 50-02-2, Dexamethasone 99614-01-4, Ondansetron hydrochloride 170729-80-3, Aprepitant

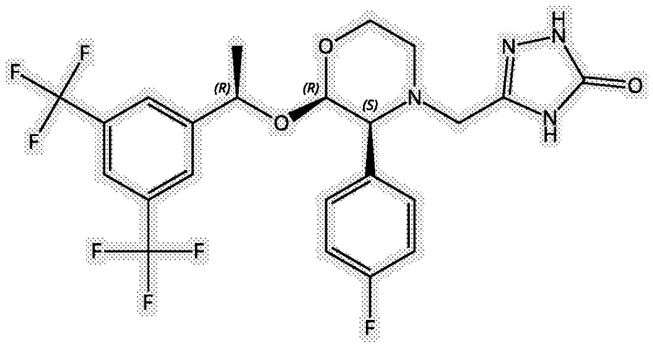
RL: PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(evaluation of Pentravan, Pentravan Plus, Phytobase, Lipovan and Pluronic Lecithin Organogel for the transdermal administration of antiemetic drugs to treat chemotherapy-induced nausea and vomiting at the hospital)

IT 9005-64-5, Tween 20
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(evaluation of Pentravan, Pentravan Plus, Phytobase, Lipovan and Pluronic Lecithin Organogel for the transdermal administration of antiemetic drugs to treat chemotherapy-induced nausea and vomiting at the hospital)

IT 170729-80-3, Aprepitant
RL: PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(evaluation of Pentravan, Pentravan Plus, Phytobase, Lipovan and Pluronic Lecithin Organogel for the transdermal administration of antiemetic drugs to treat chemotherapy-induced nausea and vomiting at the hospital)

RN 170729-80-3 CAPLUS

CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

OS.CITING REF COUNT: 14 THERE ARE 14 CAPLUS RECORDS THAT CITE THIS RECORD (15 CITINGS)

REFERENCE COUNT: 55 THERE ARE 55 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 32 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN

ACCESSION NUMBER: 2016:1723954 CAPLUS Full-text

DOCUMENT NUMBER: 172:411315

TITLE: Optimization of the Ussing chamber setup with excised rat intestinal segments for dissolution/permeation experiments of poorly soluble drugs

AUTHOR(S): Forner, Kristin; Roos, Carl; Dahlgren, David; Kesisoglou, Filippos; Konerding, Moritz A.; Mazur, Johanna; Lennernaes, Hans; Langguth, Peter

CORPORATE SOURCE: Department of Pharmaceutical Technology and Biopharmaceutics, Johannes Gutenberg University, Mainz, Germany

SOURCE: Drug Development and Industrial Pharmacy (2017), 43(2), 338-346
CODEN: DDIPD8; ISSN: 0363-9045

DIGITAL OBJECT ID: 10.1080/03639045.2016.1251449

PUBLISHER: Taylor & Francis Ltd.

DOCUMENT TYPE: Journal; (online computer file)

LANGUAGE: English

AB Prediction of the in vivo absorption of poorly sol. drugs may require simultaneous dissoln./permeation expts. In vivo predictive media have been modified for permeation expts. with Caco-2 cells, but not for excised

rat intestinal segments. The present study aimed at improving the setup of dissoln./permeation expts. with excised rat intestinal segments by assessing suitable donor and receiver media. The regional compatibility of rat intestine in Ussing chambers with modified Fasted and Fed State Simulated Intestinal Fluids (Fa/FeSSIFmod) as donor media was evaluated via several parameters that reflect the viability of the excised intestinal segments. Receiver media that establish sink conditions were investigated for their foaming potential and toxicity. Dissoln./permeation expts. with the optimized conditions were then tested for two particle sizes of the BCS class II drug aprepitant. Fa/FeSSIFmod were toxic for excised rat ileal sheets but not duodenal sheets, the compatibility with jejunal segments depended on the bile salt concn. A non-foaming receiver medium contg. bovine serum albumin (BSA) and Antifoam B was nontoxic. With these conditions, the permeation of nanosized aprepitant was higher than of the unmilled drug formulations. The compatibility of Fa/FeSSIFmod depends on the excised intestinal region. The chosen conditions enable dissoln./permeation expts. with excised rat duodenal segments. The expts. correctly predicted the superior permeation of nanosized over unmilled aprepitant that is obsd. in vivo. The optimized setup uses FaSSIFmod as donor medium, excised rat duodenal sheets as permeation membrane and a receiver medium contg. BSA and Antifoam B.

CC 63-5 (Pharmaceuticals)
Section cross-reference(s): 9

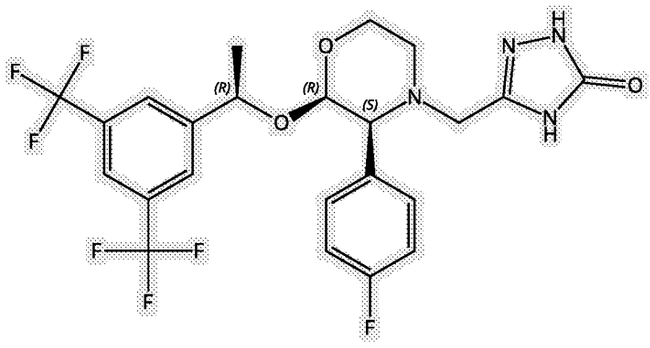
IT Lecithins
RL: MOA (Modifier or additive use); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(optimization of Ussing chamber setup with excised rat intestinal segments for dissoln./permeation expts. of poorly sol. drugs)

IT 81-81-2, Warfarin 15307-86-5, Diclofenac 29122-68-7, Atenolol 170729-80-3, Aprepitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(optimization of Ussing chamber setup with excised rat intestinal segments for dissoln./permeation expts. of poorly sol. drugs)

IT 170729-80-3, Aprepitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(optimization of Ussing chamber setup with excised rat intestinal segments for dissoln./permeation expts. of poorly sol. drugs)

RN 170729-80-3 CAPLUS

CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

OS.CITING REF COUNT: 11 THERE ARE 11 CAPLUS RECORDS THAT CITE THIS RECORD (11 CITINGS)
REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 33 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2016:1057307 CAPLUS Full-text
DOCUMENT NUMBER: 165:169358

TITLE: Difficultly-soluble drug-containing nanostructure lipid carrier pharmaceutical composition with good solubility and high bioavailability and preparation method thereof
INVENTOR(S): Jin, Yinxiu; Wang, Yuxin; Tao, Xuefen; Shi, Lei; Shen, Peipei; Xia, Nianyou
PATENT ASSIGNEE(S): Taizhou Vocational & Technical College, Peop. Rep. China
SOURCE: Faming Zhuanli Shenqing, 21pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 105708799	A	20160629	CN 2016-10056874	20160127

PRIORITY APPLN. INFO.: CN 2016-10056874 20160127
PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
CN 105708799	A	Dead	20201120

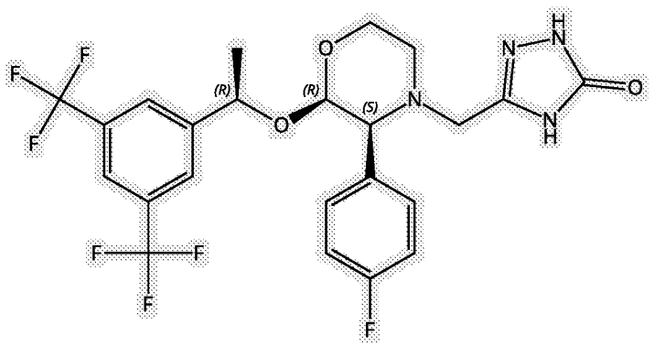
OTHER SOURCE(S): CASFORMULTNS 2016:1057307
AB The title nanostructure lipid carrier pharmaceutical compn. is prepd. from (by wt.%) difficultly-sol. drug (bezafibrate, oxcarbazepine, etc.) 0.02-1, solid lipid material (glyceryl monostearate, etc.) 0.3-15, liq. lipid material (soybean oil, etc.) 0.5-20, lipid-sol. emulsifier (lecithin and/or soybean phospholipid) 0.8-10, water-sol. emulsifier (Tween-20, etc.) 1-15 and water-sol. solvent (water, phosphate buffer soln., etc.) 39-97.38. The invention also provides a prepn. method of the nanostructure lipid carrier pharmaceutical compn. The inventive prepn. method has simple process, and good controllability and repeatability; and the inventive nanostructure lipid carrier pharmaceutical compn. contains difficultly-sol. drug, has good soly., degradability, physiol. compatibility and stability, and high bioavailability and entrapment rate, and no org. solvent residues, and can be used as drug delivery system for difficultly-sol. drug.
IPCI A61K0009-127; A61K0009-19; A61K0047-44; A61K0031-192; A61K0031-55; A61P0003-06; A61P0009-10
IPCR A61K0009-127 [I]; A61K0009-19 [I]; A61K0031-192 [I]; A61K0031-55 [I]; A61K0047-44 [I]; A61P0003-06 [I]; A61P0009-10 [I]
CC 63-6 (Pharmaceuticals)
IT Corn oil
Lecithins
Lipids
Peanut oil
Soya phospholipids
Soybean oil
Sunflower oil
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(difficultly-sol. drug-contg. nanostructure lipid carrier pharmaceutical compn. with good soly. and high bioavailability and prepn. method thereof)
IT 50-14-6, Ergocalciferol 50-24-8, Prednisolone 50-28-2, Oestradiol, biological studies 51-48-9, L-Thyroxine, biological studies 52-01-7, Spironolactone 52-86-8, Haloperidol 53-43-0, Dehydroepiandrosterone 53-86-1, Indomethacin 55-98-1, Busulfan 57-83-0, Progesterone, biological studies 66-76-2, Bishydroxycoumarin 67-20-9, Furadantin 67-45-8, Furazolidone 67-96-9, Dihydrotachysterol 67-97-0, Cholecalciferol 68-26-8, Vitamin A 76-57-3, Codeine 76-99-3, Methadone 90-82-4, Pseudoephedrine 104-31-4, Benzonatate 113-15-5, Ergotamine 113-92-8 125-84-8, Aminoglutethimide 126-07-8, Griseofulvin 127-40-2, Xanthophyll 155-97-5, Pyridostigmine 298-46-4, 5H-Dibenz[b,f]azepine-5-carboxamide 298-57-7, Cinnarizine 298-81-7, Methoxsalen 300-62-9, Amfetamine 302-79-4, Tretinoin 303-49-1, Clomipramine 303-53-7, Cyclobenzaprine 303-98-0, Coenzyme Q10 303-98-0D, Ubidecarenone, salt deriv. 321-64-2, Tacrine 359-83-1, Pentazocine 378-44-9, Betamethasone 404-86-4, Capsaicin 437-38-7, Fentanyl 443-48-1, Metronidazole 502-65-8, Lycopene 511-12-6, Dihydroergotamine 520-85-4, Medroxyprogesterone 652-67-5, Isosorbitol 911-45-5, Clomifene 1134-47-0, Baclofen 1397-89-3,

Amphotericin B 1406-16-2, Vitamin D 1406-18-4, Vitamin E 1665-48-1, Metaxalone 1951-25-3, Amiodarone 1972-08-3, Tetrahydrocannabinol 3562-63-8 4419-39-0, Beclomethasone 4759-48-2, Isotretinoin 5104-49-4, Flurbiprofen 7261-97-4, Dantrolene 7689-03-4, Camptothecin 10238-21-8, Glibenclamide 10238-21-8D, Glibenclamide, salt deriv. 10540-29-1, Tamoxifen 12001-79-5, Vitamin K 15307-86-5, Diclofenac 15574-96-6, Pizotifen 15686-51-8, Clemastine 17230-88-5, Danazol 17230-88-5D, Danazol, salt deriv. 18559-94-9, Salbutamol 19356-17-3, Calcifediol 20594-83-6, Nalbuphine 20830-75-5, Digoxin 21256-18-8, Oxaprozin 21829-25-4, Nifedipine 22916-47-8, Miconazole 23288-49-5, Probucol 25523-97-1, Dexchlorpheniramine 25812-30-0, Gemfibrozil 27203-92-5, Tramadol 28721-07-5, Oxcarbazepine 29094-61-9, Glipizide 29767-20-2, Teniposide 32222-06-3, Calcitriol 33069-62-4, Taxol 33419-42-0, Etoposide 34911-55-2, Bupropion 38304-91-5, Minoxidil 41340-25-4, Etodolac 41859-67-0, Bezafibrate 42924-53-8, Nabumetone 43200-80-2, Zopiclone 49562-28-9, Fenofibrate 49697-38-3, Rimexolone 51322-75-9, Tizanidine 51333-22-3, Budesonide 51481-61-9, Cimetidine 53123-88-9, Sirolimus 53179-11-6, Loperamide 53230-10-7, Mefloquine 54965-21-8, Albendazole 55079-83-9, Acitretin 55142-85-3, Ticlopidine 57469-82-6, Ibuprofen arginine 59467-70-8, Midazolam 59865-13-3, Cyclosporine 60142-96-3, Gabapentin 61379-65-5, Rifapentine 61869-08-7, Paroxetine 62013-04-1, Dirithromycin 63590-64-7, Terazosin 63612-50-0, Nilutamide 63675-72-9, Nisoldipine 65271-80-9, Mitoxantrone 65277-42-1, Ketoconazole 68506-86-5, Vigabatrin 69756-53-2, Halofantrine 70288-86-7, Ivermectin 72432-03-2, Miglitol 72559-06-9, Rifabutine 73590-58-6, Omeprazole 73963-72-1, Cilostazol 74103-06-3, Ketorolac 75330-75-5, Lovastatin 75706-12-6, Leflunomide 76547-98-3, Lisinopril 76824-35-6, Famotidine 76963-41-2, Nizatidine 79617-96-2, Sertraline 79794-75-5, Loratadine 79902-63-9, Simvastatin 80621-81-4, Rifaximin 81093-37-0, Pravastatin 81098-60-4, Cisapride 81103-11-9, Clarithromycin 82626-48-0, Zolpidem 83799-24-0, Fexofenadine 83881-51-0, Cetirizine 83905-01-5, Azithromycin 84057-84-1, Lamotrigine 84371-65-3, Mifepristone 84449-90-1, Raloxifene 84625-61-6, Itraconazole 85721-33-1, Ciprofloxacin 86386-73-4, Fluconazole 86541-75-5, Benazepril 88150-42-9, Amlodipine 89778-26-7, Toremifene 90357-06-5, Bicalutamide 91161-71-6, Terbinafine 93390-81-9, Fosphenytoin 93413-69-5, Venlafaxine 93479-97-1, Glimepiride 93957-54-1, Fluvastatin 95233-18-4, Atovaquone 97240-79-4, Topiramate 97322-87-7, Troglitazone 97682-44-5, Irinotecan 98319-26-7, Finasteride 101828-21-1, Butenafine 103577-45-3, Lansoprazole 103628-46-2, Sumatriptan 104987-11-3, Tacrolimus 106133-20-4, Tamsulosin 106650-56-0, Sibutramine 107753-78-6, Zafirlukast 111025-46-8, Pioglitazone 111406-87-2, Zileuton 112965-21-6, Calcipotriene 113665-84-2, Clopidogrel 114977-28-5, Docetaxel 115103-54-3, Tiagabine 117976-89-3, Rabeprazole 118292-40-3, Tazarotene 120014-06-4, Donepezil 121679-13-8, Naratriptan 122320-73-4, Rosiglitazone 123948-87-8, Topotecan 127779-20-8, Saquinavir 129497-78-5, Verteporfin 131918-61-1, Paricalcitol 133040-01-4, Eprosartan 134523-00-5, Atorvastatin 135062-02-1, Repaglinide 137862-53-4, Valsartan 138402-11-6, Irbesartan 139264-17-8, Zolmitriptan 139481-59-7, Candesartan 139755-83-2, Sildenafil 144034-80-0, Rizatriptan 144494-65-5, Tirofiban 144701-48-4, Telmisartan 145599-86-6, Cerivastatin 145941-26-0, Oprevelkin 146939-27-7, Ziprasidone 147059-72-1, Trovafloxacin 153559-49-0, Targretin 154229-19-3, Abiraterone 154598-52-4, Efavirenz 155213-67-5, Ritonavir 158747-02-5, Frovatriptan 158966-92-8, Montelukast 159989-64-7, Nelfinavir 162011-90-7, Rofecoxib 169590-42-5, Celecoxib 170729-80-3, Aprepitant 290297-26-6, Netupitant 366789-02-8, Rivaroxaban 394730-60-0, Boceprevir 402957-28-2, Telaprevir
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(difficultly-sol. drug-contg. nanostructure lipid carrier pharmaceutical compn. with good soly. and high bioavailability and prepn. method thereof)

IT 170729-80-3, Aprepitant
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(difficultly-sol. drug-contg. nanostructure lipid carrier pharmaceutical compn. with good soly. and high bioavailability and prepn. method thereof)

RN 170729-80-3 CAPLUS

CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
CN 105708799 A	CN 2016-10056874	Register|Global Dossier

L4 ANSWER 34 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2016:725430 CAPLUS Full-text
DOCUMENT NUMBER: 164:573948
TITLE: Self-microemulsifying drug delivery system for improving bioavailability of poorly soluble drug and its application
INVENTOR(S): Li, Suhua; Li, Jixi
PATENT ASSIGNEE(S): Peop. Rep. China
SOURCE: Faming Zhuanli Shenqing, 23pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 105535979	A	20160504	CN 2015-10819197	20151122
CN 105535979	B	20190625		
PRIORITY APPLN. INFO.:			CN 2015-10819197	20151122

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
CN 105535979	A	Alive	20201121
CN 105535979	B	Alive	20201121

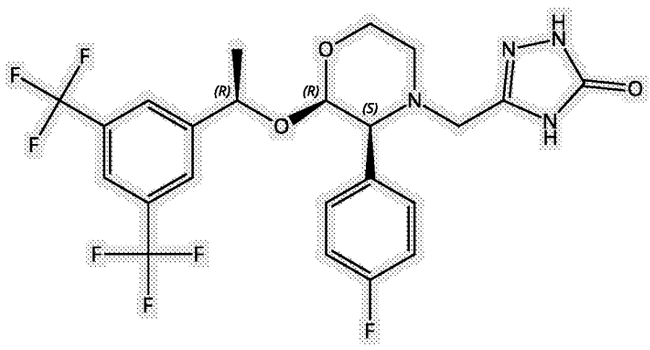
AB The present invention provides a novel self-microemulsifying drug delivery system (SEDDS), wherein the SEDDS carrier material comprises Capmul MCMs and medium-chain fatty acid-contg. oil phase and surfactant. It is suitable for loading two classes of poorly sol. drugs, including pH-dependent (weak acid, weak base drug) and non-pH-dependent (neutral drugs), greatly increases the soly. of the drug to achieve the optimal bioavailability, and has important application value in the formulation development of insol. drugs.
IPCI A61K0047-14 [I]; A61K0047-12 [I]; A61K0047-34 [I]; A61K0047-44 [I]; A61K0031-405 [I]; A61K0031-4515 [I]; A61K0031-58 [I]; A61K0047-14; A61K0047-12; A61K0047-10; A61K0047-44; A61K0031-405; A61K0031-4515; A61K0031-58
IPCR A61K0047-14 [I]; A61K0031-405 [I]; A61K0031-4515 [I]; A61K0031-58 [I]; A61K0047-12 [I]; A61K0047-34 [I]; A61K0047-44 [I]; A61K0047-14 [I]; A61K0047-10 [I]; A61K0047-44 [I]

CC 63-6 (Pharmaceuticals)
IT Acylcarnitines
Alcohols
Amino acids
Bile acids
Bile salts
Cephalins
Ceramides
Dipeptides
Ethoxylated hydrogenated castor oil
Gangliosides
Glycerides
Glycerophospholipids
Glycosphingolipids
Lecithins
Lysophosphatides
Lysophosphatidylcholines
Lysophosphatidylserines
Medium-chain fatty acids
Monoglycerides
Phosphatidic acids
Phosphatidylcholines
Phosphatidylserines
Phospholipids
Polyoxyalkylenes
Pyranosides
Sphingomyelins
Tripeptides
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(self-microemulsifying drug delivery system for improving bioavailability of poorly sol. drug and its application)
IT 50-14-6, Ergocalciferol 50-24-8, Prednisolone 50-28-2, Oestradiol, biological studies 51-48-9, L-Thyroxine, biological studies 52-01-7, Spironolactone 52-86-8, Haloperidol 53-43-0, Dehydroepiandrosterone 53-86-1, Indomethacin 55-98-1, Busulfan 57-83-0, Progestin, biological studies 66-76-2, Dicoumarol 67-20-9, Nitrofurantoin 67-45-8, Furazolidone 67-96-9, Dihydrotachysterol 67-97-0, Cholecal ciferol 68-26-8, Vitamin A 76-57-3, Codeine 76-99-3, Methadone 83-43-2, Methylprednisolone 90-82-4, Pseudoephedrine 104-31-4, Benzonatate 113-15-5, Ergotamine 113-92-8, Chlorphenamine maleate 125-84-8, Aminoglutethimide 126-07-8, Griseofulvin 127-40-2 155-97-5, Pyridostigmine 298-46-4, 5H-Dibenz[b,f]azepine-5-carboxamide 298-57-7, Cinnarizine 298-81-7, Methoxsalen 300-62-9, Amphetamine 302-79-4, Retinoic acid 303-49-1, Clomipramine 303-53-7, Cyclobenzaprine 303-98-0, Coenzyme Q10 321-64-2, Tacrine 359-83-1, Pentazocine 378-44-9, Betamethasone 404-86-4, Capsaicin 437-38-7, Fentanyl 443-48-1, Metronidazole 502-65-8, Lycopene 511-12-6, Dihydroergotamine 652-67-5, Isosorbitol 911-45-5, Clomifene 1134-47-0, Baclofen 1397-89-3, Amphotericin B 1406-16-2, Vitamin D 1406-18-4, Vitamin E 1665-48-1, Metaxalone 1951-25-3, Amiodarone 1972-08-3, Tetrahydrocannabinol 3562-63-8 4419-39-0, Beclomethasone 4759-48-2, Isotretinoin 5104-49-4, Flurbiprofen 7261-97-4, Dantrolene 7689-03-4, Camptothecin 10238-21-8, Glyburide 10540-29-1, Tamoxifen 12001-79-5, Vitamin K 15307-86-5, Diclofenac 15574-96-6, Pizotifen 15686-51-8, Clemastine 15687-27-1, Ibuprofen 17230-88-5, Danazol 18559-94-9, Salbutamol 19356-17-3, Calcifediol 20594-83-6, Nalbuphine 20830-75-5, Digoxin 21256-18-8, Oxaprozin 21829-25-4, Nifedipine 22916-47-8, Miconazole 23288-49-5, Probucol 25523-97-1, Dexchlorpheniramine 25812-30-0, Gemfibrozil 27203-92-5, Tramadol 29094-61-9, Glipizide 29767-20-2, Teniposide 32222-06-3, Calcitriol 33069-62-4, Paclitaxel 33419-42-0, Etoposide 34911-55-2, Bupropion 38304-91-5, Minoxidil 41340-25-4, Etodolac 42924-53-8, Nabumetone 43200-80-2, Zopiclone 49562-28-9, Fenofibrate 49697-38-3, Rimexolone 51322-75-9, Tizanidine 51333-22-3, Budesonide 51481-61-9, Cimetidine 53123-88-9, Sirolimus 53179-11-6, Loperamide 53230-10-7, Mefloquine 54965-21-8, Albendazole 55079-83-9, Acitretin 55142-85-3, Ticlopidine 59467-70-8, Midazolam 60142-96-3, Gabapentin 61379-65-5, Rifapentine 61869-08-7, Paroxetine 62013-04-1, Dirithromycin 63590-64-7, Terazosin 63612-50-0, Nilutamide 63675-72-9, Nisoldipine 65271-80-9, Mitoxantrone 65277-42-1, Ketoconazole 68506-86-5, Vigabatrin 69756-53-2, Halofantrine 70288-86-7, Ivermectin 72432-03-2, Miglitol

72559-06-9, Rifabutine 73590-58-6, Omeprazole 73963-72-1, Cilostazole
74103-06-3, Ketorolac 75330-75-5, Lovastatin 75706-12-6, Leflunomide
76547-98-3, Lisinopril 76824-35-6, Famotidine 76963-41-2, Nizatidine
79217-60-0, Cyclosporin 79617-96-2, Sertraline 79794-75-5, Loratadine
79902-63-9, Simvastatin 80621-81-4, Rifaximin 81093-37-0, Pravastatin
81098-60-4, Cisapride 81103-11-9, Clarithromycin 82626-48-0, Zolpidem
83799-24-0, Fexofenadine 83881-51-0, Cetirizine 83905-01-5,
Azithromycin 84057-84-1, Lamotrigine 84371-65-3, Mifepristone
84449-90-1, Raloxifene 84625-61-6, Itraconazole 85721-33-1,
Ciprofloxacin 86386-73-4, Fluconazole 86541-75-5, Benazepril
88150-42-9, Amlodipine 89778-26-7, Toremifene 90357-06-5, Bicalutamide
91161-71-6, Terbinafine 93390-81-9, Fosphenytoin 93413-69-5,
Venlafaxine 93479-97-1, Glimepiride 93957-54-1, Fluvastatin
95233-18-4, Atovaquone 97240-79-4, Topiramate 97322-87-7, Troglitazone
97682-44-5, Irinotecan 98319-26-7, Finasteride 101828-21-1, Butenafine
103577-45-3, Lansoprazole 103628-46-2, Sumatriptan 104987-11-3,
Tacrolimus 106133-20-4, Tamsulosin 106650-56-0, Sibutramine
107753-78-6, Zafirlukast 111025-46-8, Pioglitazone 111406-87-2,
Zileuton 112965-21-6, Calcipotriene 113665-84-2, Clopidogrel
114977-28-5, Docetaxel 115103-54-3, Tiagabine 117976-89-3, Rabeprazole
118292-40-3, Tazarotene 120014-06-4, Donepezil 121679-13-8,
Naratriptan 122320-73-4, Rosiglitazone 123948-87-8, Topotecan
127779-20-8, Saquinavir 129497-78-5, Verteporfin 131918-61-1,
Paricalcitol 133040-01-4, Eprosartan 134523-00-5, Atorvastatin
135062-02-1, Repaglinide 137862-53-4, Valsartan 138402-11-6,
Irbesartan 139264-17-8, Zolmitriptan 139481-59-7, Candesartan
139755-83-2, Sildenafil 144034-80-0, Rizatriptan 144494-65-5,
Tirofiban 144701-48-4, Telmisartan 145599-86-6, Cerivastatin
146939-27-7, Ziprasidone 147059-72-1, Trovafloxacin 153559-49-0,
Targretin 154229-19-3, Abiraterone 154598-52-4, Efavirenz
155213-67-5, Ritonavir 158747-02-5, Frovatriptan 158966-92-8,
Montelukast 159989-64-7, Nelfinavir 162011-90-7, Rofecoxib
169590-42-5, Celecoxib 170729-80-3, Aprepitant 290297-26-6,
Netupitant 366789-02-8, Rivaroxaban 394730-60-0, Boceprevir
402957-28-2, Telaprevir
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES
(Uses)
(self-microemulsifying drug delivery system for improving
bioavailability of poorly sol. drug and its application)

IT 170729-80-3, Aprepitant
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES
(Uses)
(self-microemulsifying drug delivery system for improving
bioavailability of poorly sol. drug and its application)

RN 170729-80-3 CAPLUS
CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phen
yl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX
NAME)



Absolute stereochemistry shown
Rotation (+)

OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD
(3 CITINGS)

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
CN 105535979 A	CN 2015-10819197	Register|Global Dossier
CN 105535979 B	CN 2015-10819197	Register|Global Dossier

L4 ANSWER 35 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2016:535017 CAPLUS Full-text
DOCUMENT NUMBER: 164:512967
TITLE: Aprepitant loaded nanocrystal lipid microcapsule for treating nausea and vomiting after chemotherapy
INVENTOR(S): Zhu, Songlin; Xiao, Yan; Meng, Qingyue; Zhao, Yongxing; Cui, Hao; Chen, Yongqiang; Fang, Shuixia; Pan, Na; Chen, Shuiku; Liang, Qian; Luo, Feng; Liu, Jinxia; Yue, Xiaohui
PATENT ASSIGNEE(S): Furen Medicines Group Co., Ltd., Peop. Rep. China; Kaifeng Pharmaceutical (Group) Co., Ltd.; Henan Furen Pharmaceutical Technology Development Co., Ltd.
ULTIMATE OWNER: FUREN MEDICINE GROUP; KAIFENG PHARMACEUTICAL GROUP; HENAN FUREN MEDICAL TECH DEV
ULTIMATE OWNER STANDARD: FUREN MEDICINE GROUP; KAIFENG PHARMACEUTICAL GROUP; HENAN FUREN MEDICAL TECH DEV
SOURCE: Faming Zhuanli Shenqing, 7pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 105456228	A	20160406	CN 2015-10928963	20151211
CN 105456228	B	20180605		

PRIORITY APPLN. INFO.: CN 2014-10814246 A 20141224
PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
CN 105456228	A	Alive	20201121
CN 105456228	B	Alive	20201121

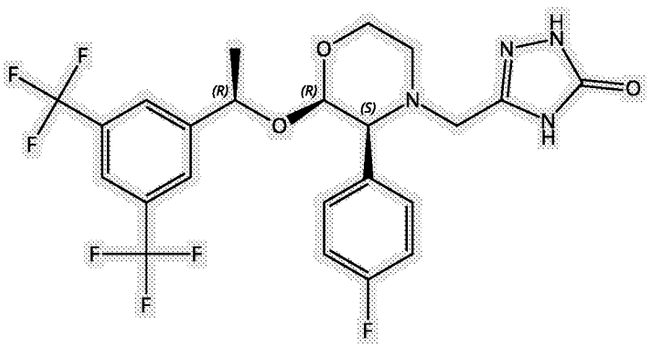
OTHER SOURCE(S): CASFORMULTNS 2016:535017
AB The present invention provides an aprepitant loaded nanocrystal lipid microcapsule, and its prepn. method is as follows: prepg. aprepitant nanocrystals with av. particle size ranging from 50 nm to 400 nm with aprepitant and stabilizer through grinding, high-speed air-jet milling or high-pressure homogenization, dispersing in water and forming a suspension; after then, after dissolving phospholipid in an org. solvent, mixing and emulsifying with the aprepitant nanocrystals suspension, subsequently removing liq. phase, drying and obtaining prepd. the aprepitant nanocrystal lipid microcapsule; wherein the particle size distribution of aprepitant nanocrystal lipid microcapsules is 10-500 μm; the stabilizer is a mixt. of one or two and more of polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer, polyvinyl pyrrolidone, hydroxypropylmethyl cellulose, poloxamer and the like; the phospholipid is a mixt. of one or two and more of soybean phospholipid, lecithin and hydrogenated phospholipid. The above-mentioned aprepitant nanocrystal lipid microcapsule has stable properties, good in vivo absorption, high bioavailability and rapid drug efficacy functions; it can be used for treating nausea and vomiting after chemotherapy.
IPCI A61K0009-50; A61K0031-5377; A61K0047-24; A61P0001-08; A61P0025-24
IPCR A61K0009-50 [I]; A61K0031-5377 [I]; A61K0047-24 [I]; A61P0001-08 [I]; A61P0025-24 [I]
CC 63-6 (Pharmaceuticals)
IT Lecithins
Phospholipids
Soya phospholipids
RL: MOA (Modifier or additive use); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aprepitant loaded nanocrystal lipid microcapsule for treating nausea and vomiting after chemotherapy)
IT 170729-80-3, Aprepitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(aprepitant loaded nanocrystal lipid microcapsule for treating nausea and vomiting after chemotherapy)

IT 170729-80-3, Aprepitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aprepitant loaded nanocrystal lipid microcapsule for treating nausea and vomiting after chemotherapy)

RN 170729-80-3 CAPLUS

CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
CN 105456228 A	CN 2015-10928963	Register|Global Dossier
CN 105456228 B	CN 2015-10928963	Register|Global Dossier

L4 ANSWER 36 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN

ACCESSION NUMBER: 2016:473657 CAPLUS Full-text
DOCUMENT NUMBER: 164:387016
TITLE: Emulsion formulations of aprepitant
INVENTOR(S): Ottoboni, Thomas B.; Han, Han
PATENT ASSIGNEE(S): Heron Therapeutics, Inc., USA
ULTIMATE OWNER: HERON THERAPEUTICS, INC.
ULTIMATE OWNER STANDARD: HERON THERAPEUTICS, INC.
SOURCE: PCT Int. Appl., 36pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2016044784	A1	20160324	WO 2015-US51050	20150918
US 20160082013	A1	20160324	US 2015-14859013	20150918
US 9808465	B2	20171107		
KR 2017056575	A	20170523	KR 2017-7008598	20150918
KR 2424837	B1	20220725		
CN 106852118	A	20170613	CN 2015-80050449	20150918
EP 3193830	A1	20170726	EP 2015-772163	20150918
EP 3193830	B1	20231101		
EP 3193830	C0	20231101		
JP 2017533183	T	20171109	JP 2017-514863	20150918
JP 6741655	B2	20200819		
US 20160206622	A1	20160721	US 2016-15083071	20160328
US 9561229	B2	20170207		
US 20170112847	A1	20170427	US 2017-15398928	20170105
US 10500208	B2	20191210		
US 20180000828	A1	20180104	US 2017-15705201	20170914
US 9974793	B2	20180522		

US 20180000829	A1	20180104	US 2017-15705208		20170914
US 9974794	B2	20180522			
JP 2019196398	A	20191114	JP 2019-137539		20190726
US 20200197404	A1	20200625	US 2019-16669262		20191030
US 10953018	B2	20210323			
US 20210186981	A1	20210624	US 2021-17194114		20210305
JP 2022092040	A	20220621	JP 2022-66236		20220413

PRIORITY APPLN. INFO.:

US 2014-62052948	P	20140919
JP 2017-514863	A3	20150918
US 2015-14859013	A1	20150918
WO 2015-US51050	W	20150918
US 2016-15083071	A1	20160328
US 2017-15398928	A1	20170105
JP 2019-137539	A3	20190726
US 2019-16669262	A1	20191030

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
WO 2016044784	A1	Dead	20201202
US 20160082013	A1	Alive	20201121
US 9808465	B2	Alive	20201120
KR 2017056575	A	Alive	20220602
KR 2424837	B1	Alive	20220811
CN 106852118	A	Transitional	20240307
EP 3193830	A1	Alive	20201201
EP 3193830	C0	Alive	20240104
JP 2017533183	T	Alive	20201121
JP 6741655	B2	Alive	20201121
US 20160206622	A1	Alive	20201120
US 9561229	B2	Alive	20201120
US 20170112847	A1	Alive	20201120
US 10500208	B2	Alive	20201120
US 20180000828	A1	Alive	20201121
US 9974793	B2	Alive	20201120
US 20180000829	A1	Alive	20201121
US 9974794	B2	Alive	20201120
JP 2019196398	A	Dead	20231026
US 20200197404	A1	Alive	20201121
US 10953018	B2	Alive	20210401
US 20210186981	A1	Alive	20231012
JP 2022092040	A	Dead	20231207

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OTHER SOURCE(S): CASFORMULTNS 2016:473657

AB Disclosed herein are novel pharmaceutical formulations of aprepitant suitable for parenteral administration including i.v. administration. Also included are formulations including both aprepitant and dexamethasone sodium phosphate. The pharmaceutical formulations are stable oil-in-water emulsions for non-oral treatment of emesis and are particularly useful for treatment of subjects undergoing cancer chemotherapy.

IPCI A61K0009-00 [I]; A61K0047-10 [I]; A61K0047-44 [I]; A61K0047-24 [I]; A61K0047-12 [I]; A61K0047-26 [I]

IPCR A61K0009-00 [I]; A61K0047-10 [I]; A61K0047-12 [I]; A61K0047-24 [I]; A61K0047-26 [I]; A61K0047-44 [I]

CC 63-6 (Pharmaceuticals)

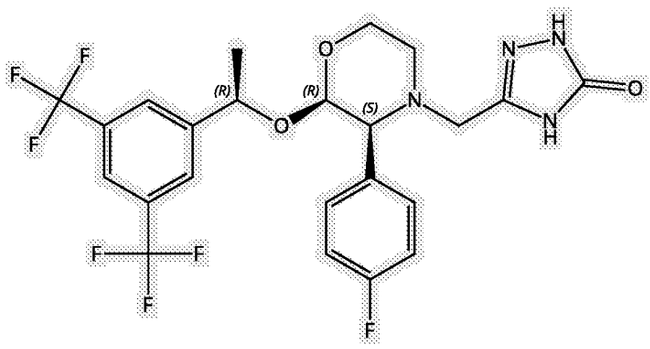
IT Alcohols
Egg yolk lecithins
Phospholipids
Soybean oil
RL: COS (Cosmetic use); BIOL (Biological study); USES (Uses)
(emulsion formulations of aprepitant)

IT 2392-39-4 170729-80-3
RL: PKT (Pharmacokinetics); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(emulsion formulations of aprepitant)

IT 170729-80-3
RL: PKT (Pharmacokinetics); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(emulsion formulations of aprepitant)

RN 170729-80-3 CAPLUS

CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
CN 106852118 A	CN 2015-80050449	Register|Global Dossier
EP 3193830 A1	EP 2015-772163	Register|Federated Reg.
EP 3193830 B1	EP 2015-772163	Register|Federated Reg.
EP 3193830 C0	EP 2015-772163	Register|Federated Reg.
JP 2017533183 T	JP 2017-514863	Register|Global Dossier
JP 6741655 B2	JP 2017-514863	Register|Global Dossier
JP 2019196398 A	JP 2019-137539	Register|Global Dossier
JP 2022092040 A	JP 2022-66236	Register|Global Dossier
KR 2017056575 A	KR 2017-7008598	Register|Global Dossier
KR 2424837 B1	KR 2017-7008598	Register|Global Dossier
US 20160082013 A1	US 2015-14859013	Register|Global Dossier
US 9808465 B2	US 2015-14859013	Register|Global Dossier
US 20160206622 A1	US 2016-15083071	Register|Global Dossier
US 9561229 B2	US 2016-15083071	Register|Global Dossier
US 10500208 B2	US 2017-15398928	Register|Global Dossier
US 20170112847 A1	US 2017-15398928	Register|Global Dossier
US 20180000828 A1	US 2017-15705201	Register|Global Dossier
US 9974793 B2	US 2017-15705201	Register|Global Dossier
US 20180000829 A1	US 2017-15705208	Register|Global Dossier
US 9974794 B2	US 2017-15705208	Register|Global Dossier
US 10953018 B2	US 2019-16669262	Register|Global Dossier
US 20200197404 A1	US 2019-16669262	Register|Global Dossier
US 20210186981 A1	US 2021-17194114	Register|Global Dossier
WO 2016044784 A1	WO 2015-US51050	Register|Global Dossier

L4 ANSWER 37 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2015:1470836 CAPLUS Full-text
DOCUMENT NUMBER: 163:403366
TITLE: Method for manufacture of nano suspension
INVENTOR(S): Wang, Yongjun; Han, Xiangfei; Xue, Peng; Wang, Jing; Jiang, Mengjuan; He, Zhonggui
PATENT ASSIGNEE(S): Shenyang Pharmaceutical University, Peop. Rep. China
SOURCE: Faming Zhuanli Shenqing, 14pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 104887626	A	20150909	CN 2015-10287997	20150529

PRIORITY APPLN. INFO.: CN 2015-10287997 20150529

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
CN 104887626	A	Dead	20201120

AB The present invention relates to a method for manuf. of nano suspension, belonging to the field of pharmaceutical prepns. The present invention utilizes an effervescent method to generate bubbles for dispersion and mixing to obtain nano-suspensions, and includes the following specific steps : mixing drug, stabilizer, the org. acid and other pharmaceutically acceptable excipients as org. phase, dissolving carbonate and other pharmaceutically acceptable excipients in water as carbonate phase, mixing the two phases, or shaking or vortex, to obtain nano suspension. The drug contg. prescription comprises drugs 1, stabilizer 0. 01-20, org. acids 0. 01 -10, carbonate 0. 01 -10 wt. parts. The carbonate is sodium carbonate, potassium carbonate, KHCO3, CaCO3, calcium bicarbonate, ammonium carbonate, etc. The org. acid is malic acid, citric acid, succinic acid, sorbic acid, formic acid, acetic acid, propionic acid. The stabilizer is PEG 1000 vitamin E succinate, Tween, Span, poloxamer, etc. The drug is insol. anticancer drug, insol. antifungal drug, insol. antimicrobial agent, hypotensive drug, etc. The present invention significantly improves the soly. and dissoln. rate of poorly sol. drugs, thereby increases the bioavailability of poorly sol. drugs.

IPCI A61K0009-10 [I]; A61K0047-12 [I]; A61K0047-04 [I]; A61K0045-00 [I]

IPCR A61K0009-10 [I]; A61K0045-00 [I]; A61K0047-04 [I]; A61K0047-12 [I]

CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1

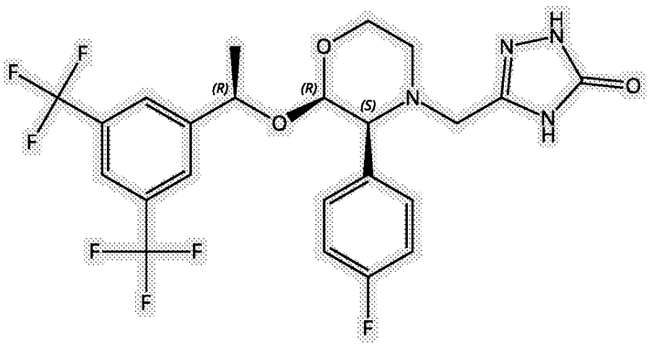
IT Amino acids
Carbonates
Ethoxylated hydrogenated castor oil
Fatty acids
Fatty alcohols
Gelatins
Lecithins
Organic acids
Phospholipids
Polyoxyalkylenes
Taxanes
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(method for manuf. of pharmaceutical nano suspension)

IT 50-02-2, Dexamethasone 52-01-7, Spirolactone 443-48-1, Metronidazole 595-33-5, Megestrol acetate 1397-89-3, Amphotericin B 7689-03-4, Camptothecin 9002-96-4, TPGS 10238-21-8, Glibenclamide 15307-86-5, Diclofenac 15687-27-1, Ibuprofen 16773-42-5, Ornidazole 23593-75-1, Clotrimazole 29767-20-2, Teniposide 33069-62-4, Taxol 33419-42-0, Etoposide 39562-70-4, Nitrendipine 53123-88-9, Sirolimus 55985-32-5, Nicardipine 66085-59-4, Nimodipine 79794-75-5, Loratadine 84625-61-6, Itraconazole 93479-97-1, Glimepiride 103577-45-3, Lansoprazole 104987-11-3, Tacrolimus 170729-80-3, Aprepitant 183133-96-2, Cabazitaxel 199739-10-1, Paliperidone palmitate
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(method for manuf. of pharmaceutical nano suspension)

IT 170729-80-3, Aprepitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(method for manuf. of pharmaceutical nano suspension)

RN 170729-80-3 CAPLUS

CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
CN 104887626 A	CN 2015-10287997	Register|Global Dossier

L4 ANSWER 38 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2015:1390403 CAPLUS Full-text
DOCUMENT NUMBER: 163:369597
TITLE: Compositions of pentosan polysulfate salts for oral administration and methods of use
INVENTOR(S): Parsons, C. Lowell; Goldberg, Michael; Meenan, Christopher P.
PATENT ASSIGNEE(S): Urigen Pharmaceuticals, Inc., USA
ULTIMATE OWNER: PLATINUM MONTAUR LIFE SCIENCES
ULTIMATE OWNER STANDARD: PLATINUM MONTAUR LIFE SCIENCES
SOURCE: PCT Int. Appl., 248pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2015127416	A1	20150827	WO 2015-US17205		20150224
CA 2949480	A1	20150827	CA 2015-2949480		20150224
AU 2015218642	A1	20161006	AU 2015-218642		20150224
EP 3110427	A1	20170104	EP 2015-751441		20150224
KR 2017003527	A	20170109	KR 2016-7026610		20150224
CN 106456662	A	20170222	CN 2015-80022057		20150224
JP 2017512757	T	20170525	JP 2016-554267		20150224
US 20170189443	A1	20170706	US 2016-15121312		20160824
PRIORITY APPLN. INFO.:			US 2014-61943824	P	20140224
			WO 2015-US17205	W	20150224

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
WO 2015127416	A1	Dead	20201201
CA 2949480	A1	Dead	20220428
AU 2015218642	A1	Dead	20210318
EP 3110427	A1	Dead	20210729
KR 2017003527	A	Alive	20201121
CN 106456662	A	Dead	20201121
JP 2017512757	T	Alive	20201120
US 20170189443	A1	Dead	20210324

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): MARPAT 163:369597; CASFORMULTNS 2015:1390403
AB The invention is directed to a pharmaceutical compn. comprising: (1) a therapeutically effective quantity of sodium pentosan polysulfate; (2) a quantity of a penetration enhancer sufficient to improve the bioavailability of the sodium pentosan polysulfate; and (3) optionally, a

pharmaceutically acceptable carrier and to methods for the oral administration of sodium pentosan polysulfate with improved bioavailability for the treatment of interstitial cystitis and other urinary tract diseases and conditions. Such compns. and methods allow the administration of sodium pentosan polysulfate at lower dosages to reduce the frequency and severity of side effects.

IPCI A61K0031-715 [I]; C07H0005-10 [I]; A61K0047-14 [I]; A61P0019-02 [I]

IPCR A61K0031-715 [I]; A61K0047-14 [I]; A61P0019-02 [I]; C07H0005-10 [I]

CC 1-12 (Pharmacology)

IT Acrylic polymers
Acylcarnitines
Amino acids
Bile salts
Bone morphogenetic protein 7
Bone sialoproteins
Cartilage oligomeric matrix protein
Collagen type I
Collagen type II
Collagen type IX
Collagen type XI
Collagens
Crown compounds
Dendrimers
Diglycerides
Estrogens
Fatty acids
Insulin-like growth factor-binding protein 3
Lecithins
Matrix proteins
Medium-chain fatty acids
Monoclonal antibodies
Monoglycerides
Opioids
Osteocalcins
Osteonectin
Osteopontin
Peptides
Polyanhydrides
Polyoxyalkylenes
Proteins
Salicylates
Steroidal hormones
Sulfonanilides
Terpenes
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. of pentosan polysulfate salts for oral administration and methods of use)

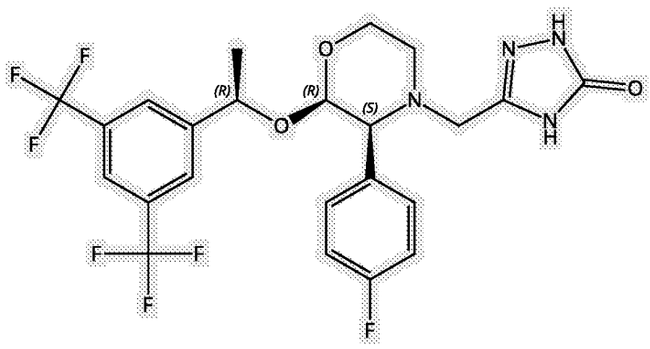
IT 15866-90-7, Metastat 15880-03-2 16011-96-4, 2-Iminopiperidine hydrochloride 16067-69-9, Strontium benzenesulfonate 16088-89-4, Strontium maleate 16139-18-7, Aminoguanidine hydrochloride 18847-18-2 19767-45-4, Mesna 19878-22-9 19982-08-2, Memantine 20093-91-8 20594-83-6, Nalbuphine 21084-57-1, 8-(Phthalimido)caprylic acid 21256-18-8, Oxaprozin 21463-31-0, 2-Amino-5,6-dihydro-6-methyl-4H-1,3-thiazine hydrochloride 22059-21-8, 1-Aminocyclopropane-1-carboxylic acid 22071-15-4, Ketoprofen 22204-53-1, Naproxen 22410-94-2 22494-42-4, Diflunisal 22834-47-5 24314-23-6 24339-95-5 25087-26-7 25087-26-7D, derivs. 25322-68-3 25496-72-4 25518-54-1 25587-34-2 26009-03-0, Poly[oxy(1-oxo-1,2-ethanediyl)] 26023-30-3, Poly[oxy(1-methyl-2-oxo-1,2-ethanediyl)] 26100-51-6, Polylactic acid 26124-68-5, Polyglycolic acid 26171-23-3, Tolmetin 26615-21-4, Zotepine 26864-56-2, Penfluridol 27203-92-5, Tramadol 27261-86-5 27540-07-4 27638-00-2 28945-89-3, 3-(3-Ethoxyphenyl)propanoic acid 28945-91-7, 3-(3-Butoxyphenyl)propanoic acid 29679-58-1, Fenoprofen 30762-02-8, 4-(Cyclopentyloxy)benzoic acid 31477-60-8, Ormeloxifene 33369-31-2, Zomepirac 34346-01-5 34816-55-2, Moxestrol 35197-20-7 36322-90-4, Piroxicam 36330-86-6 36440-58-1 36978-49-1 38194-50-2, Sulindac 39860-99-6, Pipotiazine 40182-75-0, Strontium citrate 40391-99-9 40472-00-2, Strontium succinate 41340-25-4, Etodolac 41839-80-9 42408-82-2, Butorphanol 42907-92-6 42907-93-7 43218-50-4 47739-98-0, Clocapramine 49594-75-4 50700-72-6,

Vecuronium 51036-98-7 51333-22-3, Budesonide 51803-78-2, Nimesulide
52240-14-9 52349-26-5 52485-79-7, Buprenorphine 52888-70-7,
3-(3-Phenoxyphenyl)propanoic acid 53583-79-2, Sultopride 53597-27-6,
Fendosal 53648-55-8, Dezocine 53716-49-7, Carprofen 53772-83-1,
Zuclopenthixol 57648-21-2, Timiperone 57821-78-0 59122-46-2,
Misoprostol 59227-89-3 59804-37-4, Tenoxicam 59865-13-3,
Cyclosporine 60118-07-2, Endorphin 61126-74-7 61126-76-9
63471-88-5 64228-79-1, Atracurium 64779-07-3 64779-14-2
65576-45-6, Asenapine 66644-81-3, Veralipride 67763-96-6, Insulin like
growth factor-1 68047-06-3, 4-Hydroxy-tamoxifen 68134-81-6,
Gacyclidine 71125-38-7, Meloxicam 71675-85-9, Amisulpride
74103-06-3, Ketorolac 75221-40-8, [4-(Cyclohexylmethoxy)phenyl]acetic
acid 75221-43-1 75272-39-8, Nemonapride 75706-12-6, Leflunomide
77086-21-6, Dizocilpine 77599-17-8, Panomifene 78994-23-7,
Levormeloxifene 79055-68-8 79669-11-7, 3-(4-Isopropoxyphenyl)propanoic
acid 79778-41-9, Neridronate 80125-14-0, Remoxipride 81093-37-0,
Pravastatin 81109-85-5 82413-20-5, Droloxifene 83015-26-3,
Atomoxetine 84449-90-1, Raloxifene 86111-26-4, Zindoxifene
89326-69-2, 5-(4-Ethylphenyl)pentanoic acid 89419-40-9, Mosapramine
89750-15-2, Glucagon like peptide-2 89778-26-7, Toremifene 89987-06-4,
Tiludronate 93957-54-1, Fluvastatin 98007-99-9 98774-23-3,
Tesmilifene 100759-29-3 100944-08-9 101253-68-3 102676-47-1,
Fadrozole 103735-76-8, erythro-MEA 103987-16-2 105462-24-6,
Risedronate 106266-06-2, Risperidone 106516-24-9, Sertindole
107868-30-4, Exemestane 108179-99-3 110347-85-8, Selfotel
110931-77-6 111974-69-7, Quetiapine 112809-51-5, Letrozole
114084-78-5, Ibandronate 115767-74-3, TAT-59 116057-68-2
116057-75-1, Idoxifene 117910-70-0 117928-94-6, Rapastinel
118072-93-8, Zoledronic acid 119431-25-3, Eliprodil 120511-73-1,
Anastrozole 121368-58-9, Olpadronate 122004-99-3 123663-49-0, T-614
124937-51-5, Tolterodine 124937-52-6, Detrol 128298-28-2, Remacemide
128607-22-7, Ospemifene 129318-43-0 129453-61-8, Fulvestrant
129612-87-9, Miproxifene 129722-12-9, Aripiprazole 129731-10-8,
Vorozole 129948-69-2 130370-59-1, GI-129471 130370-60-4, Batimastat
131123-76-7, 5,7-Dichlorokynurenic acid 131692-21-2 132539-06-1,
Olanzapine 132810-10-7, Blonanserin 133454-47-4, Iloperidone
133814-18-3, Doxacurium 134523-00-5, Atorvastatin 135459-87-9,
Strontium ranelate 136013-76-8, 2-(Cyclopropylmethoxy)benzoic acid
136553-81-6, BQ-123 136982-36-0, CP-99994 137159-92-3, Aptiganel
137945-48-3, CT-3 138330-18-4, Incadronate 141620-66-8 142880-36-2,
Ilomastat 144598-75-4, Paliperidone 145599-86-6, Cerivastatin
146490-38-2 146939-27-7, Ziprasidone 147536-97-8, Bosentan
148215-77-4, 2-(Cyclopentyloxy)benzoic acid 148700-85-0, L-733060
150403-89-7 150915-41-6, Perospirone 153322-05-5, Lanicemine
153438-49-4, RPR-100893 154039-60-8, Marimastat 155383-07-6, SDZ-PTS
893 156161-89-6, BQ-788 156806-79-0 157116-68-2 157116-71-7
158089-95-3, S-2474 158860-95-8, 3-(Cyclohexylmethoxy)benzoic acid
158860-99-2, 3-(Cyclopentyloxy)benzoic acid 159190-44-0 162011-90-7,
Rofecoxib 162752-13-8, 3-(4-Propylphenyl)propanoic acid 165536-41-4,
MDL-103323 168158-16-5, KB-R-7785 168266-90-8, Vofopitant
168980-06-1 168980-07-2 168980-08-3 168980-09-4 168980-10-7
168980-12-9 168980-13-0 169590-41-4, Deracoxib 169590-42-5,
Celecoxib 169799-04-6, MMI-270 169799-44-4, Keratin sulfate
170277-31-3, Infliximab 170566-84-4, Lanepitant 170713-75-4
170729-80-3, Aprepitant 172673-20-0, Fosaprepitant
173937-91-2, Atrasentan 175033-36-0, NCX4016 177036-94-1, Ambrisentan
177172-49-5 177653-18-8 177653-31-5 177653-36-0 177653-53-1
177653-62-2 177653-65-5 179545-77-8, Tanomastat 180064-38-4
180384-57-0, Tezosentan
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)
(compns. of pentosan polysulfate salts for oral administration and
methods of use)

IT 170729-80-3, Aprepitant
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)
(compns. of pentosan polysulfate salts for oral administration and
methods of use)

RN 170729-80-3 CAPLUS

CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phen
yl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX
NAME)



Absolute stereochemistry shown
Rotation (+)

OS.CITING REF COUNT: 4 THERE ARE 4 CAPLUS RECORDS THAT CITE THIS RECORD (4 CITINGS)
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
AU 2015218642 A1	AU 2015-218642	Register
CA 2949480 A1	CA 2015-2949480	Register
CN 106456662 A	CN 2015-80022057	Register|Global Dossier
EP 3110427 A1	EP 2015-751441	Register|Federated Reg.
JP 2017512757 T	JP 2016-554267	Register|Global Dossier
KR 2017003527 A	KR 2016-7026610	Register|Global Dossier
US 20170189443 A1	US 2016-15121312	Register|Global Dossier
WO 2015127416 A1	WO 2015-US17205	Register|Global Dossier

L4 ANSWER 39 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2015:865407 CAPLUS Full-text
DOCUMENT NUMBER: 162:663467
TITLE: Orally disintegrating porous film comprising pharmacological active ingredient and method for preparing the same
INVENTOR(S): Oh, Dong Hoon; Lee, Jin Hoo; Lee, So Yi; Kang, Jun Hyuk; Lim, Chae Yun; Jung, Kyung Tae; Yeon, Kyu Jeong; Park, Jin Gyu
PATENT ASSIGNEE(S): Seoul Pharma. Co., Ltd., S. Korea
ULTIMATE OWNER: SEOUL PHARMA. CO., LTD.
ULTIMATE OWNER STANDARD: SEOUL PHARMA. CO., LTD.
SOURCE: PCT Int. Appl., 30pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Korean
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

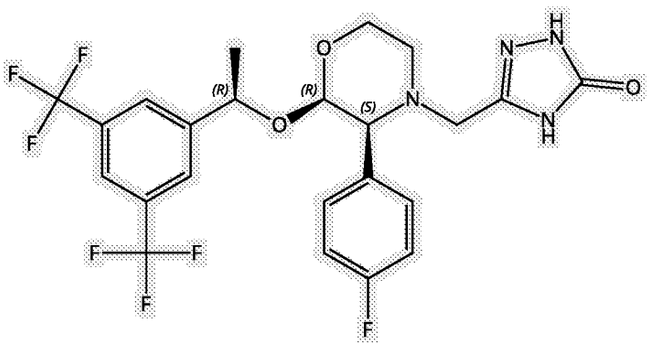
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2015072684	A1	20150521	WO 2014-KR10293	20141030
KR 1407922	B1	20140617	KR 2013-138040	20131114
CN 105873572	A	20160817	CN 2014-80071821	20141030
EP 3069716	A1	20160921	EP 2014-861454	20141030
US 20160279071	A1	20160929	US 2016-15036784	20160513
PRIORITY APPLN. INFO.:			KR 2013-138040 A	20131114
			WO 2014-KR10293 W	20141030

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
WO 2015072684	A1	Dead	20201202
KR 1407922	B1	Dead	20201121
CN 105873572	A	Dead	20201121

EP 3069716 A1 Dead 20201203
US 20160279071 A1 Dead 20201121
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASFORMULTNS 2015:865407
AB The present invention relates to an orally disintegrating porous film and a method for prepg. the same, the film comprising a foaming agent, a foam stabilizing agent, a plasticizer, and pharmacol. active ingredient. The orally disintegrating porous film according to the present invention has micropores within the film and phys. properties suitable for a film, so that the film has an effect of significantly improving the dissoln. rate of a drug and has good processability since the film can be easily prepd. at low cost and through a simplified prepn. method.
IPCI A61K0009-70 [I]; A61P0003-10 [I]; A61P0003-04 [I]
IPCR A61K0009-70 [I]; A61P0003-04 [I]; A61P0003-10 [I]
CC 63-6 (Pharmaceuticals)
IT Alditols
Enzymes
Hormones, animal
Lecithins
Medium-chain fatty acids
Polyoxyalkylenes
Vitamins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(orally disintegrating porous film comprising pharmacol. active substance and its manufg. method)
IT 50-02-2, Dexamethasone 50-58-8, Phendimetrazine tartrate 50-81-7, L-Ascorbic acid, biological studies 54-11-5, Nicotine 55-63-0, Nitroglycerin 56-81-5, Glycerin, biological studies 56-81-5D, Glycerin, fatty acid esters 57-50-1D, Sucrose, fatty acid esters 57-55-6, Propylene glycol, biological studies 58-08-2, Caffeine, biological studies 61-76-7, Phenylephrine hydrochloride 90-84-6, Diethylpropion 94-09-7, Benzocaine 102-76-1, Triacetin 103-90-2, Acetaminophen 113-92-8 123-03-5, Cetylpyridinium chloride 124-90-3, Oxycodone hydrochloride 125-69-9, Dextromethorphan bromide 147-24-0, Diphenhydramine hydrochloride 345-78-8, Pseudoephedrine hydrochloride 357-08-4, Naloxone hydrochloride 437-38-7, Fentanyl 562-10-7 569-65-3, Meclizine 797-63-7, Levonorgestrel 1134-47-0, Baclofen 1197-21-3, Phentermine hydrochloride 1508-65-2, Oxybutynin hydrochloride 2216-51-5, L-Menthol 7232-21-5, Metoclopramide hydrochloride 7384-98-7, Propylene glycol dicaprylate 8050-81-5, Simethicone 9000-30-0, Guar gum 9000-40-2, Locust bean gum 9000-69-5, Pectin 9003-20-7, Polyvinyl acetate 9004-65-3, Hydroxypropyl methyl cellulose 9005-25-8, Starch, biological studies 9005-25-8D, Starch, derivs. 9005-32-7, Alginic acid 9057-02-7, Pullulan 11138-66-2, Xanthan gum 12441-09-7D, Sorbitan, fatty acid esters 14611-52-0, Selegiline hydrochloride 15307-86-5, Diclofenac 15687-27-1, Ibuprofen 16679-58-6, Desmopressin 22071-15-4, Ketoprofen 22232-71-9, Mazindol 23828-92-4, Ambroxol hydrochloride 25322-68-3, Polyethylene oxide 27848-84-6, Nicergoline 28911-01-5, Triazolam 28981-97-7, Alprazolam 31565-12-5, Propylene glycol monocaprylate 34552-83-5, Loperamide hydrochloride 37220-82-9, Glycerol oleate 41100-52-1, Memantine hydrochloride 51481-61-9, Cimetidine 52485-79-7, Buprenorphine 56211-40-6, Torasemide 59729-32-7, Citalopram hydrobromide 64461-82-1, Tizanidine hydrochloride 66357-59-3, Ranitidine hydrochloride 71125-38-7, Meloxicam 72797-41-2, Tianeptine 73590-58-6, Omeprazole 76824-35-6, Famotidine 77883-43-3, Doxazosin mesylate 79794-75-5, Loratadine 82248-59-7, Atomoxetine hydrochloride 82626-48-0, Zolpidem 83480-29-9, Voglibose 83881-52-1, Cetirizine hydrochloride 84057-84-1, Lamotrigine 87333-19-5, Ramipril 90729-43-4, Ebastine 93479-97-1, Glimepiride 97240-79-4, Topiramate 99614-01-4, Ondansetron hydrochloride 99614-02-5, Ondansetron 100299-08-9, Pemirolast potassium 100643-71-8, Desloratadine 103577-45-3, Lansoprazole 103628-46-2, Sumatriptan 106133-20-4, Tamsulosin 106266-06-2, Risperidone 109889-09-0, Granisetron 112885-41-3, Mosapride 119356-77-3, Dapoxetine 120011-70-3, Donepezil hydrochloride 129722-12-9, Aripiprazole 132539-06-1, Olanzapine 132907-72-3, Ramosetron hydrochloride 139264-17-8, Zolmitriptan 139755-83-2, Sildenafil 140462-76-6, Olopatadine hydrochloride 144034-80-0, Rizatriptan 144689-63-4, Olmesartan medoxomil 151767-02-1, Montelukast sodium 153439-40-8, Fexofenadine hydrochloride 158966-92-8, Montelukast 170729-80-3, Aprepitant 171596-29-5, Tadalafil 171599-83-0, Sildenafil citrate 219861-08-2, Escitalopram oxalate

224785-91-5, Vardenafil hydrochloride 242478-38-2, Solifenacin succinate
246852-12-0, Amlodipine mesylate 268203-93-6, Udenafil 286930-03-8,
Fesoterodine fumarate 385367-47-5, Tarafenacin 823178-28-5
862189-96-6
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(orally disintegrating porous film comprising pharmacol. active
substance and its manufg. method)
IT 170729-80-3, Aprepitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(orally disintegrating porous film comprising pharmacol. active
substance and its manufg. method)
RN 170729-80-3 CAPLUS
CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phen
yl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX
NAME)



Absolute stereochemistry shown
Rotation (+)

OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD
(1 CITINGS)
REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
CN 105873572 A	CN 2014-80071821	Register|Global Dossier
EP 3069716 A1	EP 2014-861454	Register|Federated Reg.
KR 1407922 B1	KR 2013-138040	Register|Global Dossier
US 20160279071 A1	US 2016-15036784	Register|Global Dossier
WO 2015072684 A1	WO 2014-KR10293	Register|Global Dossier

L4 ANSWER 40 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2014:2053394 CAPLUS Full-text
DOCUMENT NUMBER: 162:85982
TITLE: Lipid, protein, and/or cationic molecule coated pharmaceutically active particles and compositions comprising same
INVENTOR(S): Chawrai, Suresh; Prasad, Sudhanand; Bajaj, Kirti
PATENT ASSIGNEE(S): Vyome Biosciences Pvt. Ltd., India
ULTIMATE OWNER: VYOME THERAPEUTICS LIMITED
ULTIMATE OWNER STANDARD: Vyome
SOURCE: PCT Int. Appl., 221pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2014195872	A1	20141211	WO 2014-IB61925	20140603
CA 2914583	A1	20141211	CA 2014-2914583	20140603
CA 2914583	C	20190618		

AU 2014276460	A1	20151224	AU 2014-276460		20140603
IL 242916	A	20160131	IL 2014-242916		20140603
KR 2016015335	A	20160212	KR 2015-7037272		20140603
KR 1814895	B1	20180104			
CN 105407718	A	20160316	CN 2014-80042031		20140603
CN 105407718	B	20190104			
EP 3003031	A1	20160413	EP 2014-739231		20140603
JP 2016523232	T	20160808	JP 2016-517716		20140603
BR 112015030501	A2	20170725	BR 2015-112015030501		20140603
NZ 714817	A	20170728	NZ 2014-714817		20140603
US 20160128944	A1	20160512	US 2015-14895738		20151203
MX 2015016675	A	20160715	MX 2015-16675		20151203
IN 2015CN07967	A	20160831	IN 2015-CN7967		20151224
AU 2017203374	A1	20170608	AU 2017-203374		20170519
AU 2018282407	A1	20190117	AU 2018-282407		20181221
PRIORITY APPLN. INFO.:			IN 2013-DE1684	A	20130604
			AU 2014-276460	A3	20140603
			WO 2014-IB61925	W	20140603
			AU 2017-203374	A3	20170519

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
WO 2014195872	A1	Dead	20201201
CA 2914583	A1	Dead	20221013
CA 2914583	C	Dead	20221013
AU 2014276460	A1	Dead	20201121
KR 2016015335	A	Alive	20201121
KR 1814895	B1	Alive	20201121
CN 105407718	A	Dead	20221117
CN 105407718	B	Dead	20221117
EP 3003031	A1	Dead	20210715
JP 2016523232	T	Alive	20201121
BR 112015030501	A2	Alive	20210729
NZ 714817	A	Dead	20210820
US 20160128944	A1	Dead	20210408
MX 2015016675	A	Alive	20201120
AU 2017203374	A1	Alive	20201121
AU 2018282407	A1	Dead	20210708

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OTHER SOURCE(S): CASFORMULTNS 2014:2053394

AB The invention provides species of lipid, protein, and/or cationic mol. coated active agents and compns. comprising the coated particles. The compns. can be personal care compns. such as anti-dandruff shampoo or conditioner, skin care compns., creams, gels, toothpastes, mouth washes, and chewing gums.

IPCI A01N0025-12 [I]; A01N0025-34 [I]; A01N0037-06 [I]; A01N0043-12 [I]; A01N0043-40 [I]; A01N0057-12 [I]; A01N0059-16 [I]; A61K0008-11 [I]; A61K0008-49 [I]; A61Q0005-00 [I]; A61K0031-44 [I]; A61Q0019-00 [I]; A61K0009-00 [I]; A61K0031-496 [I]

IPCR A01N0025-34 [I]; A01N0025-12 [I]; A01N0037-06 [I]; A01N0043-12 [I]; A01N0043-40 [I]; A01N0057-12 [I]; A01N0059-16 [I]; A61K0008-11 [I]; A61K0008-49 [I]; A61K0009-00 [I]; A61K0031-44 [I]; A61K0031-496 [I]; A61Q0005-00 [I]; A61Q0019-00 [I]

CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 62

IT Actins
Albumins
Alkaloids
Aminoglycosides
Androgens
Antibodies and Immunoglobulins
Apricot kernel oil
Avocado oil
Blood proteins
Carbapenems
Carbohydrates
Caseins
Citronella oil
Coal tar
Coconut oil
Collagen hydrolyzates
Collagens

Conchiolins
Corticosteroids
Curcuminoids
Echinocandins
Egg yolk lecithins
Elastins
Estrogens
Ethoxylated hydrogenated castor oil
Fibroin
Fibronectins
Flavanoids
Flavonoids
Fructooligosaccharides
Galactooligosaccharides
Gelatin hydrolyzates
Glycerolipids
Glycerophospholipids
Glycopeptides
Glycosaminoglycans
Hemoglobins
Hydrocarbon oils
Immunoglobulin fragments
Indoles
Integrins
Keratins
Ketolides
Lactalbumins
Lipids
Macrolides
Milk proteins
Neem oil
Oligosaccharides
Oxazolidinones
Palmarosa oil
Paraffin oils
Peppermint oil
Peptide analogs
Peptides
Phosphatidic acids
Phosphatidylcholines
Phosphatidylethanolamines
Phosphatidylinositol 4,5-bisphosphate
Phosphatidylinositol 4-phosphate
Phosphatidylinositols
Phosphatidylinositols
Phosphatidylserines
Phospholipids
Podophyllum (resin)
Polyamines
Polyamines (nonpolymeric)
Polyketides
Polyoxyalkylenes
Polysaccharides
Progestogens
Pyrethroids
Reticulin
Retinoids
Sericin hydrolyzates
Sericins
Soya lecithins
Soybean proteins
Sphingolipids
Sterols
Sulfonamides
Sunflower oil
Sweet orange peel oil
Tetracyclines
Tocopherols
Zeins
β-Lactams
RL: COS (Cosmetic use); THU (Therapeutic use); BIOL (Biological study);
USES (Uses)

(lipid and protein and/or cationic mol. coated pharmaceutically active particles and compns. comprising same)

IT 84625-61-6, Itraconazole 84957-29-9, Cefpirome 85233-19-8, 1,2-Bis(o-aminophenoxy)ethane-N,N,N',N'-tetraacetic acid 85441-61-8, Quinapril 85622-93-1, Temozolomide 85650-52-8, Mirtazapine 85721-33-1, Ciprofloxacin 86003-55-6, Nikkomycin 86386-73-4, Fluconazole 86541-75-5, Benazepril 86697-97-4, Sensomer CT-250 87061-04-9 87239-81-4, Cefpodoxime proxetil 87848-99-5, Acrivastine 88040-23-7, Cefepime 88150-42-9, Amlodipine 89365-50-4, Salmeterol 91161-71-6, Terbinafine 91374-21-9, Ropinirole 91832-40-5, Cefdinir 92348-62-4, Hydroxycaprylic acid 92665-29-7, Cefprozil 93413-69-5, Venlafaxine 95058-81-4, Gemcitabine 96036-03-2, Meropenem 97321-87-4 97519-39-6, Ceftibuten 97682-44-5, Irinotecan 98079-51-7, Lomefloxacin 99011-02-6, Imiquimod 99592-32-2, Sertaconazole 99614-02-5, Ondansetron 100643-71-8, Desloratadine 100986-85-4, Levofloxacin 101828-21-1, Butenafine 103060-53-3, Daptomycin 103577-45-3, Lansoprazole 103775-14-0, Moexiprilat 104227-87-4, Famciclovir 104632-26-0, Pramipexole 105462-24-6, Risedronic acid 105956-97-6, Clinafloxacin 106133-20-4, Tamsulosin 106266-06-2, Risperidone 106392-12-5, Poloxamer 407 106516-24-9, Sertindole 106650-56-0, Sibutramine 106685-40-9, Adapalene 107233-08-9, Cevimeline 107753-78-6, Zafirlukast 108319-06-8, Temafloxacin 110871-86-8, Sparfloxacin 111025-46-8, Pioglitazone 111974-69-7, Quetiapine 112362-50-2, Dalfopristin 112809-51-5, Letrozole 112811-59-3, Gatifloxacin 112965-21-6, Calcipotriene 113170-55-1 113665-84-2, Clopidogrel 113775-47-6, Dexmedetomidine 113806-05-6, Olopatadine 114798-26-4, Losartan 115103-54-3, Tiagabine 115256-11-6, Dofetilide 115956-12-2, Dolasetron 116539-59-4, Duloxetine 117467-28-4, Cefditoren pivoxil 117976-89-3, Rabeprazole 118292-40-3, Tazarotene 119141-88-7, Esomeprazole 119914-60-2, Grepafloxacin 120014-06-4, Donepezil 120138-50-3, Quinupristin 120279-96-1, Dorzolamide 120511-73-1, Anastrozole 121028-76-0 121708-81-4 123441-03-2, Rivastigmine 124937-51-5, Tolterodine 127045-41-4, Pazufloxacin 127254-12-0, Sitafloxacin 128196-01-0, Escitalopram 129618-40-2, Nevirapine 129639-79-8 129722-12-9, Aripiprazole 132539-06-1, Olanzapine 132781-92-1 134678-17-4, Lamivudine 135729-61-2, Palonosetron 136470-78-5, Abacavir 136817-59-9, Delavirdine 137234-62-9, Voriconazole 138402-11-6, Irbesartan 139264-17-8, Zolmitriptan 139755-83-2, Sildenafil 141388-76-3, Besifloxacin 142340-99-6, Adefovir dipivoxil 143322-58-1, Eletriptan 143491-57-0, Emtricitabine 144034-80-0, Rizatriptan 144377-73-1, Linoleamidopropyl PG-dimonium chloride phosphate 144494-65-5, Tirofiban 144689-63-4, Olmesartan medoxomil 144701-48-4, Telmisartan 145040-37-5, Candesartan cilexetil 145158-71-0, Tegaserod 146939-27-7, Ziprasidone 147059-72-1, Trovafloxacin 150378-17-9, Indinavir 151096-09-2, Moxifloxacin 151319-34-5, Zaleplon 151581-81-6, Pradimicin 152459-95-5, Imatinib 154323-57-6, Almotriptan 154592-20-8, Copper pyrithione 156259-68-6, Capmul MCM 159989-64-7, Nelfinavir 161465-32-3, Elaidolinolenyl alcohol 162011-90-7, Rofecoxib 162808-62-0, Caspofungin 165800-03-3, Linezolid 166663-25-8, Anidulafungin 169590-42-5, Celecoxib 170729-80-3, Aprepitant 171228-49-2, POsaconazole 171596-29-5, Tadalafil 175357-18-3 175463-14-6, Gemifloxacin 177933-73-2D, AMP (acrylate polymer), allyl methacrylate copolymer 179463-17-3, Cancidas 182760-06-1, Ravuconazole 184475-35-2, Gefitinib 187949-02-6, Albaconazole 188627-80-7, Eptifibatide 191114-48-4, Telithromycin 194804-75-6 195868-36-1, Phenyl trimethicone 198904-31-3, Atazanavir 201341-05-1, Tenofovir disoproxil 201531-68-2D, Pyridazinone, dimorpholino deriv. 220222-14-0, Lithium pyrithione 220222-18-4, Strontium pyrithione 224785-90-4, Vardenafil 226256-56-0, Cinacalcet 235114-32-6, Micafungin 241479-67-4, Isavuconazole 313998-09-3, Gold pyrithione 351420-48-9 351420-50-3 374629-79-5 433711-29-6, Carbopol Aqua SF 1 463965-85-7, Behentrimonium methosulfate 506412-91-5 577746-42-0 608514-56-3 830331-83-4 881038-57-9, Zinc selenide sulfide 915764-71-5 951216-62-9 1477911-63-9, Dimethicone PEG-7 Isostearate 1639929-04-6

RL: COS (Cosmetic use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(lipid and protein and/or cationic mol. coated pharmaceutically active particles and compns. comprising same)

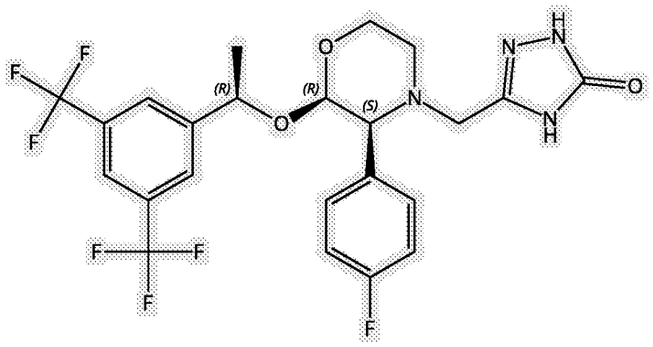
IT 170729-80-3, Aprepitant

RL: COS (Cosmetic use); THU (Therapeutic use); BIOL (Biological study);

USES (Uses)
(lipid and protein and/or cationic mol. coated pharmaceutically active particles and compns. comprising same)

RN 170729-80-3 CAPLUS

CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

OS.CITING REF COUNT: 16 THERE ARE 16 CAPLUS RECORDS THAT CITE THIS RECORD (17 CITINGS)

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
AU 2014276460 A1	AU 2014-276460	Register
AU 2017203374 A1	AU 2017-203374	Register
AU 2018282407 A1	AU 2018-282407	Register
BR 112015030501 A2	BR 2015-112015030501	Register
CA 2914583 A1	CA 2014-2914583	Register
CA 2914583 C	CA 2014-2914583	Register
CN 105407718 A	CN 2014-80042031	Register|Global Dossier
CN 105407718 B	CN 2014-80042031	Register|Global Dossier
EP 3003031 A1	EP 2014-739231	Register|Federated Reg.
IL 242916 A	IL 2014-242916	Register
IN 2015CN07967 A	IN 2015-CN7967	Register
JP 2016523232 T	JP 2016-517716	Register|Global Dossier
KR 1814895 B1	KR 2015-7037272	Register|Global Dossier
KR 2016015335 A	KR 2015-7037272	Register|Global Dossier
MX 2015016675 A	MX 2015-16675	Register
NZ 714817 A	NZ 2014-714817	Register
US 20160128944 A1	US 2015-14895738	Register|Global Dossier
WO 2014195872 A1	WO 2014-IB61925	Register|Global Dossier

L4 ANSWER 41 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN

ACCESSION NUMBER: 2014:1944702 CAPLUS Full-text

DOCUMENT NUMBER: 164:453599

TITLE: Statistical investigation of simulated intestinal fluid composition on the equilibrium solubility of biopharmaceutics classification system class II drugs

AUTHOR(S): Khadra, Ibrahim; Zhou, Zhou; Dunn, Claire; Wilson, Clive G.; Halbert, Gavin

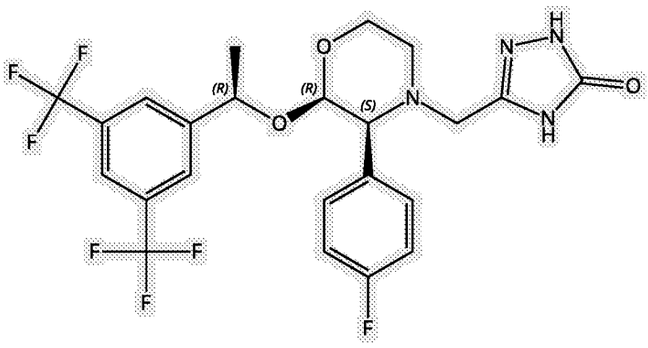
CORPORATE SOURCE: Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow, G4 0RE, UK

SOURCE: European Journal of Pharmaceutical Sciences (2015), 67, 65-75
CODEN: EPSCED; ISSN: 0928-0987

DIGITAL OBJECT ID: 10.1016/j.ejps.2014.10.019

PUBLISHER: Elsevier B.V.

DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
AB A drug's soly. and dissoln. behavior within the gastrointestinal tract is a key property for successful administration by the oral route and one of the key factors in the biopharmaceutics classification system. This property can be detd. by investigating drug soly. in human intestinal fluid (HIF) but this is difficult to obtain and highly variable, which has led to the development of multiple simulated intestinal fluid (SIF) recipes. Using a statistical design of expt. (DoE) technique this paper has investigated the effects and interactions on equil. drug soly. of seven typical SIF components (sodium taurocholate, lecithin, sodium phosphate, sodium chloride, pH, pancreatin and sodium oleate) within concn. ranges relevant to human intestinal fluid values. A range of poorly sol. drugs with acidic (naproxen, indomethacin, phenytoin, and piroxicam), basic (aprepitant, carvedilol, zafirlukast, tadalafil) or neutral (fenofibrate, griseofulvin, felodipine and probucol) properties have been investigated. The equil. soly. results detd. are comparable with literature studies of the drugs in either HIF or SIF indicating that the DoE is operating in the correct space. With the exception of pancreatin, all of the factors individually had a statistically significant influence on equil. soly. with variations in magnitude of effect between the acidic and basic or neutral compds. and drug specific interactions were evident. Interestingly for the neutral compds. pH was the factor with the second largest soly. effect. Around one third of all the possible factor combinations showed a significant influence on equil. soly. with variations in interaction significance and magnitude of effect between the acidic and basic or neutral compds. The least no. of significant media component interactions were noted for the acidic compds. with three and the greatest for the neutral compds. at seven, with again drug specific effects evident. This indicates that a drug's equil. soly. in SIF is influenced depending upon drug type by between eight to fourteen individual or combinations of media components with some of these drug specific. This illustrates the complex nature of these fluids and provides for individual drugs a visualisation of the possible soly. envelope within the gastrointestinal tract, which may be of importance for modeling in vivo behavior. In addn. the results indicate that the design of expt. approach can be employed to provide greater detail of drug soly. behavior, possible drug specific interactions and influence of variations in gastrointestinal media components due to disease. The approach is also feasible and amenable to adaptation for high throughput screening of drug candidates.
CC 63-5 (Pharmaceuticals)
IT 53-86-1, Indomethacin 57-41-0, Phenytoin 126-07-8, Griseofulvin 22204-53-1, Naproxen 23288-49-5, Probucol 36322-90-4, Piroxicam 49562-28-9, Fenofibrate 72509-76-3, Felodipine 72956-09-3, Carvedilol 107753-78-6, Zafirlukast 170729-80-3, Aprepitant 171596-29-5, Tadalafil
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(statistical investigation of simulated intestinal fluid compn. on equil. soly. of biopharmaceutics classification system class II drugs)
IT 170729-80-3, Aprepitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(statistical investigation of simulated intestinal fluid compn. on equil. soly. of biopharmaceutics classification system class II drugs)
RN 170729-80-3 CAPLUS
CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

OS.CITING REF COUNT: 53 THERE ARE 53 CAPLUS RECORDS THAT CITE THIS RECORD (53 CITINGS)
REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 42 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2014:1014062 CAPLUS Full-text
DOCUMENT NUMBER: 161:132468
TITLE: Orally disintegrating film comprising pharmacologically active substance and its manufacturing method
INVENTOR(S): Oh, Dong Hun; Lee, Jin Hu; Lee, So I.; Kang, Jun Hyeok; Lim, Chae Yun; Jung, Gyeong Tae; Yeon, Gyu Jeong; Park, Jin Gyu
PATENT ASSIGNEE(S): Seoul Pharmaceutical Co., Ltd., S. Korea
ULTIMATE OWNER: SEOUL PHARMA. CO., LTD.
ULTIMATE OWNER STANDARD: SEOUL PHARMA. CO., LTD.
SOURCE: Repub. Korea, 15pp.
CODEN: KRXXFC
DOCUMENT TYPE: Patent
LANGUAGE: Korean
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
KR 1407922	B1	20140617	KR 2013-138040	20131114
WO 2015072684	A1	20150521	WO 2014-KR10293	20141030
CN 105873572	A	20160817	CN 2014-80071821	20141030
EP 3069716	A1	20160921	EP 2014-861454	20141030
US 20160279071	A1	20160929	US 2016-15036784	20160513

PRIORITY APPLN. INFO.: KR 2013-138040 A 20131114
WO 2014-KR10293 W 20141030

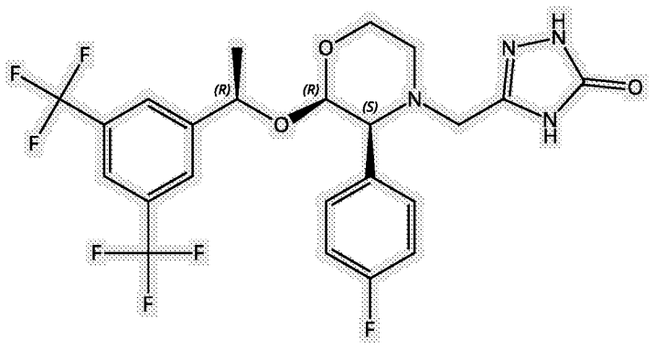
PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
KR 1407922	B1	Dead	20201121
WO 2015072684	A1	Dead	20201202
CN 105873572	A	Dead	20201121
EP 3069716	A1	Dead	20201203
US 20160279071	A1	Dead	20201121

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASFORMULTNS 2014:1014062
AB The title film has porosity of 10-35%, and contains more than one bubbling agent selected from nonionic surfactant, cationic surfactant, anionic surfactant and zwitterionic surfactant, more than one bubble stabilizer selected from pullulan, hydroxypropyl Me cellulose, polyvinyl acetate, polyethylene oxide, xanthan gum, guar gum, locust bean gum, starch, starch deriv., pectin, pectin hydrolyzate, alginic acid and alginic acid hydrolyzate, more than one plasticizer selected from glycerin, glycerol oleate, medium chain fatty acid, polyethylene glycol, propylene glycol, propylene glycol monocaprylate, propylene glycol dicaprylate, sugar, sugar

alc. and triacetin, and pharmacol. active substance.
IPCI A61K0009-70 [I]; A61P0003-10 [I]; A61P0003-04 [I]
IPCR A61K0009-70 [I]; A61P0003-04 [I]; A61P0003-10 [I]
CC 63-6 (Pharmaceuticals)
IT Alditols
Enzymes
Hormones, animal
Lecithins
Medium-chain fatty acids
Polyoxyalkylenes
Vitamins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(orally disintegrating porous film comprising pharmacol. active substance and its manufg. method)
IT 50-02-2, Dexamethasone 50-58-8, Phendimetrazine tartrate 50-81-7, L-Ascorbic acid, biological studies 54-11-5, Nicotine 55-63-0, Nitroglycerin 56-81-5, Glycerin, biological studies 56-81-5D, Glycerin, fatty acid esters 57-50-1, Sugar, biological studies 57-50-1D, Sucrose, fatty acid esters 57-55-6, Propylene glycol, biological studies 58-08-2, Caffeine, biological studies 61-76-7, Phenylephrine hydrochloride 90-84-6, Diethylpropion 94-09-7, Benzocaine 102-76-1, Triacetin 103-90-2, Acetaminophen 113-92-8 123-03-5, Cetylpyridinium chloride 124-90-3, Oxycodone hydrochloride 125-69-9, Dextromethorphan bromide 147-24-0, Diphenhydramine hydrochloride 345-78-8, Pseudoephedrine hydrochloride 357-08-4, Naloxone hydrochloride 437-38-7, Fentanyl 562-10-7 569-65-3, Meclizine 797-63-7, Levonorgestrel 1134-47-0, Baclofen 1197-21-3, Phentermine hydrochloride 1508-65-2, Oxybutynin hydrochloride 2216-51-5, L-Menthol 7232-21-5, Metoclopramide hydrochloride 7384-98-7, Propylene glycol dicaprylate 8050-81-5, Simethicone 9000-30-0, Guar gum 9000-40-2, Locust bean gum 9000-69-5, Pectin 9003-20-7, Polyvinyl acetate 9004-65-3, Hydroxypropyl methyl cellulose 9005-25-8, Starch, biological studies 9005-25-8D, Starch, derivs. 9005-32-7, Alginic acid 9057-02-7, Pullulan 11138-66-2, Xanthan gum 12441-09-7D, Sorbitan, fatty acid esters 14611-52-0, Selegiline hydrochloride 15307-86-5, Diclofenac 15687-27-1, Ibuprofen 16679-58-6, Desmopressin 22071-15-4, Ketoprofen 22232-71-9, Mazindol 23828-92-4, Ambroxol hydrochloride 25322-68-3, Polyethylene oxide 27848-84-6, Nicergoline 28911-01-5, Triazolam 28981-97-7, Alprazolam 31565-12-5, Propylene glycol monocaprylate 34552-83-5, Loperamide hydrochloride 37220-82-9, Glycerol oleate 41100-52-1, Memantine hydrochloride 51481-61-9, Cimetidine 52485-79-7, Buprenorphine 56211-40-6, Torasemide 59729-32-7, Citalopram hydrobromide 64461-82-1, Tizanidine hydrochloride 66357-59-3, Ranitidine hydrochloride 71125-38-7, Meloxicam 72797-41-2, Tianeptine 73590-58-6, Omeprazole 76824-35-6, Famotidine 77883-43-3, Doxazosin mesylate 79794-75-5, Loratadine 82248-59-7, Atomoxetine hydrochloride 83480-29-9, Voglibose 83881-52-1, Cetirizine hydrochloride 84057-84-1, Lamotrigine 87333-19-5, Ramipril 90729-43-4, Ebastine 93479-97-1, Glimepiride 97240-79-4, Topiramate 99614-01-4, Ondansetron hydrochloride 99614-02-5, Ondansetron 100299-08-9, Pemirolast potassium 100643-71-8, Desloratadine 103577-45-3, Lansoprazole 103628-46-2, Sumatriptan 106133-20-4, Tamsulosin 106266-06-2, Risperidone 109889-09-0, Granisetron 112885-41-3, Mosapride 119356-77-3, Dapoxetine 120011-70-3, Donepezil hydrochloride 129722-12-9, Aripiprazole 132539-06-1, Olanzapine 132907-72-3, Ramosetron hydrochloride 139264-17-8, Zolmitriptan 139755-83-2, Sildenafil 140462-76-6, Olopatadine hydrochloride 144034-80-0, Rizatriptan 144689-63-4, Olmesartan medoxomil 151767-02-1, Montelukast sodium 153439-40-8, Fexofenadine hydrochloride 158966-92-8, Montelukast 170729-80-3, Aprepitant 171596-29-5, Tadalafil 171599-83-0, Sildenafil citrate 219861-08-2, Escitalopram oxalate 224785-91-5, Vardenafil hydrochloride 242478-38-2, Solifenacin succinate 246852-12-0, Amlodipine mesylate 268203-93-6, Udenafil 286930-03-8, Fesoterodine fumarate 385367-47-5, Tarafenacin 823178-28-5 862189-96-6
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(orally disintegrating porous film comprising pharmacol. active substance and its manufg. method)
IT 170729-80-3, Aprepitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(orally disintegrating porous film comprising pharmacol. active

substance and its manufg. method)
RN 170729-80-3 CAPLUS
CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (4 CITINGS)

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
CN 105873572 A	CN 2014-80071821	Register|Global Dossier
EP 3069716 A1	EP 2014-861454	Register|Federated Reg.
KR 1407922 B1	KR 2013-138040	Register|Global Dossier
US 20160279071 A1	US 2016-15036784	Register|Global Dossier
WO 2015072684 A1	WO 2014-KR10293	Register|Global Dossier

L4 ANSWER 43 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2014:38255 CAPLUS Full-text
DOCUMENT NUMBER: 160:166366
TITLE: Preparation of stable injectable pharmaceutical compositions of neurokinin 1 receptor antagonist
INVENTOR(S): Karavas, Evangelos; Koutris, Efthimos; Bikiaris, Dimitrios; Chatidou, Sotiria; Diakidou, Amalia; Barmpalexis, Panagiotis; Konstanti, Louiza; Minioti, Katerina
PATENT ASSIGNEE(S): Pharmathen S.A., Greece
ULTIMATE OWNER: PARTNERS GROUP HOLDING AG
ULTIMATE OWNER STANDARD: Partners Group
SOURCE: PCT Int. Appl., 24pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2014005606	A1	20140109	WO 2012-EP2854	20120706
EP 2866797	A1	20150506	EP 2012-756353	20120706
EP 2866797	B1	20200429		
RS 60599	B1	20200831	RS 2020-846	20120706
ES 2798103	T3	20201209	ES 2012-756353	20120706
US 20150165045	A1	20150618	US 2014-14412147	20141230
US 20200237920	A1	20200730	US 2020-16851779	20200417

PRIORITY APPLN. INFO.:

EP 2012-756353	A3	20120706
WO 2012-EP2854	W	20120706
US 2014-14412147	A1	20141230

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE

WO 2014005606	A1	Dead	20201202
EP 2866797	A1	Indeterminate	20201106
EP 2866797	B1	Indeterminate	20201107
RS 60599	B1	Alive	20201121
ES 2798103	T3	Alive	20201217
US 20150165045	A1	Dead	20220105
US 20200237920	A1	Dead	20231109

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OTHER SOURCE(S): CASFORMULTNS 2014:38255

AB The present invention relates to a controlled release sterile injectable formulation in the form of soln., suspension or sol-gel formulation for i.m. or s.c. administration comprising a therapeutically effective amt. of a neurokinin 1 receptor antagonist, in particular aprepitant or fosaprepitant or pharmaceutical acceptable salts, derivs. or metabolites thereof. It also relates to a process for developing such formulations. Thus, an aq. ready-to-use soln. comprised fosaprepitant dimeglumine 142.7, and HPMC-K100 6.7 g/L and water for injection qs to 1 L.

IPCI A61K0031-165 [I]; A61K0009-00 [I]

IPCR A61K0009-00 [I]; A61K0031-165 [I]

CC 63-6 (Pharmaceuticals)

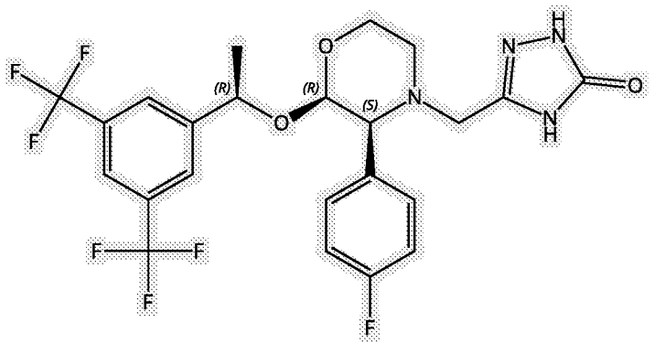
IT Castor oil
Cottonseed oil
Gelatins
Lecithins
Polymers
Polyoxyalkylenes
Sesame oil
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. of stable injectable pharmaceutical compns. of neurokinin 1 receptor antagonist)

IT 170729-80-3, Aprepitant 172673-20-0 265121-04-8, Fosaprepitant dimeglumine
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. of stable injectable pharmaceutical compns. of neurokinin 1 receptor antagonist)

IT 170729-80-3, Aprepitant
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. of stable injectable pharmaceutical compns. of neurokinin 1 receptor antagonist)

RN 170729-80-3 CAPLUS

CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

OS.CITING REF COUNT: 4 THERE ARE 4 CAPLUS RECORDS THAT CITE THIS RECORD (4 CITINGS)

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

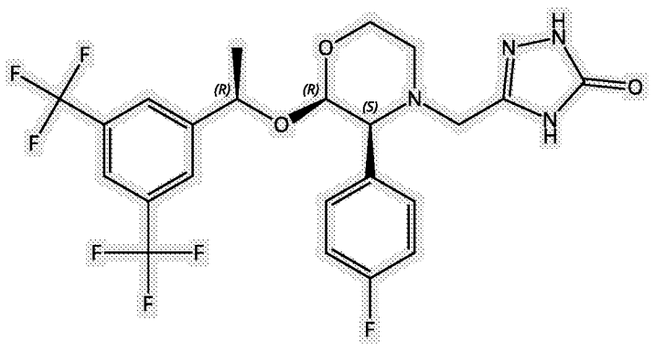
LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
EP 2866797 A1	EP 2012-756353	Register|Federated Reg.
EP 2866797 B1	EP 2012-756353	Register|Federated Reg.
ES 2798103 T3	ES 2012-756353	Register
RS 60599 B1	RS 2020-846	Register
US 20150165045 A1	US 2014-14412147	Register|Global Dossier
US 20200237920 A1	US 2020-16851779	Register|Global Dossier
WO 2014005606 A1	WO 2012-EP2854	Register|Global Dossier

L4 ANSWER 44 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2013:496643 CAPLUS Full-text
DOCUMENT NUMBER: 159:140262
TITLE: Preparation of aprepitant emulsion for intravenous injection
AUTHOR(S): Zhou, Wei; Chen, Fei; Chen, Ning; Mao, Ke
CORPORATE SOURCE: School of Pharmaceutical, Jiangsu Provincial Institute of Materia Medica, Nanjing University of Technology, Nanjing, Jiangsu Province, 211816, Peop. Rep. China
SOURCE: Zhongguo Yiyao Gongye Zazhi (2012), 43(12), 1003-1006
CODEN: ZYGZEA; ISSN: 1001-8255
PUBLISHER: Zhongguo Yiyao Gongye Zazhi Bianjibu
DOCUMENT TYPE: Journal
LANGUAGE: Chinese

AB The formulation of aprepitant emulsion for i.v. injection was optimized by single factor test and orthogonal design. The properties, such as appearance, particle size, ζ potential and stability of the product were investigated. The results showed that the type and amt. of emulsifier as well as the amt. of oleic acid had the greater effect on stability. The optimal formulation of aprepitant emulsion was as follows: aprepitant was 0.25%, soybean oil was 15%, egg yolk lecithin ESO was 2.5% and oleic acid was 0.125%. The appearance of the product was ivory. The av. particle size, PDI, centrifugal stability const. (Ke), ζ potential, pH value and drug content of the product before and after sterilization were (215.71±1.26) and (220.3±0.53) nm, 0.203±0.016 and 0.210±0.009, 0.21±0.01 and 0.34±0.01, (-37.5±0.2) and (-37.6±0.5) mV, 7.21±0.23 and 7.31±0.30, (101.03±0.89)% and (101.12±1.20)%, resp.

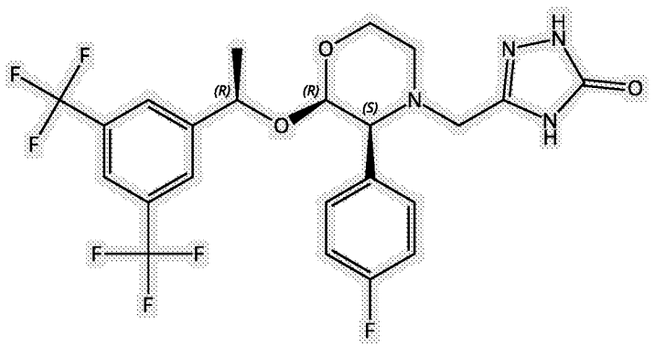
CC 63-6 (Pharmaceuticals)
IT Egg yolk lecithins
Soybean oil
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(prepn. of aprepitant emulsion for i.v. injection)
IT 170729-80-3, Aprepitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. of aprepitant emulsion for i.v. injection)
IT 170729-80-3, Aprepitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. of aprepitant emulsion for i.v. injection)
RN 170729-80-3 CAPLUS
CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

L4 ANSWER 45 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2010:1100829 CAPLUS Full-text
DOCUMENT NUMBER: 153:415489
TITLE: Simulating Fasted Human Intestinal Fluids: Understanding the Roles of Lecithin and Bile Acids
AUTHOR(S): Soederlind, Erik; Karlsson, Eva; Carlsson, Anders; Kong, Rui; Lenz, Anna; Lindborg, Sara; Sheng, Jennifer J.
CORPORATE SOURCE: Pharmaceutical Development, AstraZeneca, Moelndal, Swed.
SOURCE: Molecular Pharmaceutics (2010), 7(5), 1498-1507
CODEN: MPOHBP; ISSN: 1543-8384
DIGITAL OBJECT ID: 10.1021/mp100144v
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The purpose of this work is to evaluate the roles of lecithin and bile salts in a new generation of fasted simulated small intestinal fluid (FaSSIF-II), thus enhancing the closer mimic of simulated fluids to the real human intestinal fluids (HIF) in drug discovery and drug product development. To assess the effects of lecithin in FaSSIF-II, soly. studies were conducted at 37 °C using four media including first generation simulated intestinal fluid (FaSSIF-I), FaSSIF-II, phosphate pH 6.5 buffer, and HIF. A total of 24 model compds. representing a wide range of biopharmaceutic properties were included. The drug soly. values measured in the FaSSIF-II were compared with those in FaSSIF-I, pH 6.5 buffer and HIF. To assess the effects of bile acids, soly. was measured for 4 compds. in the FaSSIF-I contg. five different bile acids of various concns. The lecithin concn. in the FaSSIF-II is lowered from 0.75 mM to 0.2 mM. The results suggested that the FaSSIF-II is a better medium to reflect HIF, compared with pH 6.5 phosphate buffer and FaSSIF-I. Soly. of neutral compds. including atovaquone, carbamazepine, cyclosporine, danazol, diethylstilbestrol, felodipine, griseofulvin and probucol in FaSSIF-II showed improvement in predicting the in vivo soly. The relative std. deviation (SD) of soly. measurement in FaSSIF-II is comparable with FaSSIF-I. For the acidic and basic tested compds., the FaSSIF-II performs similarly to the FaSSIF-I. Exptl. results showed that the level of bile salts typically is less than 5 mM under fasted state. Among the five studied bile acids, the conjugation (glycine or taurine) has no impact on the drug solubilization, while there may be a minimal effect of the degree of hydroxylation of the steroid ring system on solubilization. The lecithin concn. of 0.2 mM in FaSSIF-II has been demonstrated to closely represent HIF, for both neutral and ionizable compds. In the compn. of simulated intestinal fluids, the structure of bile acids has minimal effect, providing the flexibility of choosing one bile salt to represent complex in vivo bile acids.
CC 63-5 (Pharmaceuticals)
ST intestine fluid human lecithin bile acid drug soly
IT Artificial intestinal juice
Dissolution
Human
Hydroxylation
Intestinal juice
Solubility
Solubilization
(simulating fasted human intestinal fluids, roles of lecithin and bile acids)
IT Bile acids
Egg yolk lecithins
Phosphatidylcholines
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(simulating fasted human intestinal fluids, roles of lecithin and bile acids)
IT 81-24-3, Taurocholic acid 145-42-6, Sodium taurocholate 360-65-6, Glycodeoxycholic acid 475-31-0, Glycocholic acid 516-50-7, Taurodeoxycholic acid 640-79-9, Glycochenodeoxycholic acid
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(simulating fasted human intestinal fluids, roles of lecithin and bile acids)

IT 56-53-1, Diethylstilbestrol 57-66-9, Probenecid 58-32-2, Dipyridamole
68-26-8, Retinol 81-81-2, Warfarin 126-07-8, Griseofulvin 298-46-4,
Carbamazepine 530-78-9, Flufenamic acid 599-79-1, Sulfasalazine
1951-25-3, Amiodarone 15307-86-5, Diclofenac 17230-88-5, Danazol
23288-49-5, Probucol 29094-61-9, Glipizide 36322-90-4, Piroxicam
50679-08-8, Terfenadine 51803-78-2, Nimesulide 59865-13-3, Cyclosporin
A 65277-42-1, Ketoconazole 72509-76-3, Felodipine 72956-09-3,
Carvedilol 95233-18-4, Atovaquone 138402-11-6, Irbesartan
168273-06-1, Rimonabant 170729-80-3, Aprepitant
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES
(Uses)
(simulating fasted human intestinal fluids, roles of lecithin
and bile acids)
IT 170729-80-3, Aprepitant
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES
(Uses)
(simulating fasted human intestinal fluids, roles of lecithin
and bile acids)
RN 170729-80-3 CAPLUS
CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phen
yl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX
NAME)



Absolute stereochemistry shown
Rotation (+)

OS.CITING REF COUNT: 24 THERE ARE 24 CAPLUS RECORDS THAT CITE THIS
RECORD (24 CITINGS)
REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 46 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2006:142759 CAPLUS Full-text
DOCUMENT NUMBER: 144:239925
TITLE: Solid carriers for improved delivery of active
ingredients containing surfactants and glycerides
INVENTOR(S): Patel, Mahesh
PATENT ASSIGNEE(S): USA
ULTIMATE OWNER: LIPOCINE INC.
ULTIMATE OWNER STANDARD: Lipocine
SOURCE: U.S. Pat. Appl. Publ., 35 pp., Cont.-in-part of U.S.
Ser. No. 428,341.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 13
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20060034937	A1	20060216	US 2005-196805	20050802
US 6248363	B1	20010619	US 1999-447690	19991123
CA 2706113	A1	20010531	CA 2000-2706113	20001122
US 20030064097	A1	20030403	US 2001-800593	20010306
US 6569463	B2	20030527		

US 20030215496	A1	20031120	US 2003-428341		20030501
US 6923988	B2	20050802			
WO 2007018943	A2	20070215	WO 2006-US27159		20060712
WO 2007018943	A3	20090507			
US 20090074859	A1	20090319	US 2008-326711		20081202
JP 2012116863	A	20120621	JP 2012-29635		20120214
US 20140357586	A1	20141204	US 2014-14460188		20140814
US 20150224130	A9	20150813			
US 20150273067	A1	20151001	US 2015-14713692		20150515
US 20180125978	A1	20180510	US 2017-15625764		20170616
US 20200061191	A1	20200227	US 2019-16289565		20190228
US 20210008212	A1	20210114	US 2020-16917731		20200630
PRIORITY APPLN. INFO.:			US 1999-447690	A3	19991123
			US 2001-800593	A1	20010306
			US 2003-428341	A2	20030501
			CA 2000-2391923	A3	20001122
			JP 2001-539423	A3	20001122
			US 2002-159601	A2	20020530
			US 2005-196805	A	20050802
			US 2008-326711	A1	20081202
			US 2014-14460188	A1	20140814
			US 2017-15625764	A1	20170616
			US 2019-16289565	A1	20190228

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
US 20060034937	A1	Dead	20201107
US 6248363	B1	Dead	20201107
CA 2706113	A1	Dead	20201121
US 20030064097	A1	Dead	20201106
US 6569463	B2	Dead	20201106
US 20030215496	A1	Dead	20201106
US 6923988	B2	Dead	20201107
WO 2007018943	A2	Dead	20201201
WO 2007018943	A3	Dead	20201201
US 20090074859	A1	Dead	20201107
JP 2012116863	A	Alive	20201121
US 20140357586	A1	Dead	20201107
US 20150224130	A9	Dead	20201107
US 20150273067	A1	Dead	20201107
US 20180125978	A1	Dead	20201106
US 20200061191	A1	Dead	20201106
US 20210008212	A1	Dead	20210128

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OTHER SOURCE(S): CASFORMULTNS 2006:142759

AB The present invention provides solid pharmaceutical compns. for improved delivery of a wide variety of pharmaceutical active ingredients contained therein or sep. administered. In one embodiment, the solid pharmaceutical compn. includes a solid carrier, the solid carrier including a substrate and an encapsulation coat on the substrate. The encapsulation coat can include different combinations of pharmaceutical active ingredients, hydrophilic surfactant, lipophilic surfactants and triglycerides. In another embodiment, the solid pharmaceutical compn. includes a solid carrier, the solid carrier being formed of different combinations of pharmaceutical active ingredients, hydrophilic surfactants, lipophilic surfactants and triglycerides. The compns. of the present invention can be used for improved delivery of hydrophilic or hydrophobic pharmaceutical active ingredients, such as drugs, nutritional agents, cosmeceuticals and diagnostic agents. For example, particles contained glyburide, PEG stearate, glycerol monolaurate, and Nonpareil seed.

INCL 424497000

IPCI A61K0009-50 [I]; A61K0009-16 [I]

IPCR A61K0009-50 [I]; A61K0009-16 [I]

NCL 424/497.000

CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 18, 62

IT Lecithins
RL: COS (Cosmetic use); FFD (Food or feed use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hydrogenated; solid carriers for improved delivery of active ingredients contg. surfactants and glycerides)

IT Diglycerides

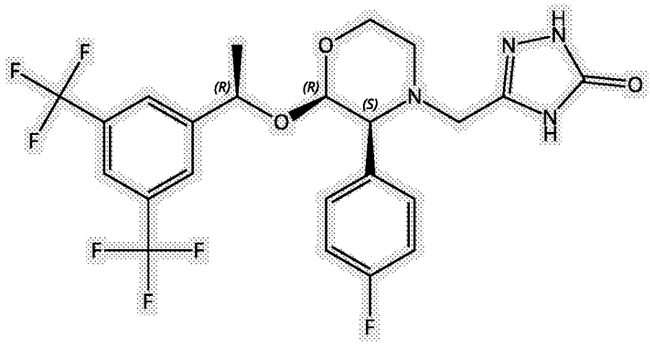
Ethoxylated hydrogenated castor oil
Glycerides
Lecithins
Oligopeptides
Peptides
Polyoxyalkylenes
Safflower oil
Sterols
RL: COS (Cosmetic use); FFD (Food or feed use); THU (Therapeutic use);
BIOL (Biological study); USES (Uses)
(solid carriers for improved delivery of active ingredients contg. surfactants and glycerides)

IT 50-35-1, Thalidomide 50-49-7, Imipramine 52-01-7, Spironolactone
52-86-8, Haloperidol 53-03-2, Prednisone 53-39-4, Oxandrolone
57-83-0, Progesterone, biological studies 67-20-9, Nitrofurantoin
81-24-3 83-44-3, Deoxycholic acid 87-69-4D, Tartaric acid, esters
112-80-1, 9-Octadecenoic acid (9Z)-, biological studies 124-07-2,
Octanoic acid, biological studies 145-42-6, Sodium taurocholate
151-41-7, Lauryl sulfate 302-79-4, Tretinoin 303-98-0, Coenzyme Q10
321-64-2, Tacrine 334-48-5, Decanoic acid 357-70-0, Galantamine
511-12-6, Dihydroergotamine 541-15-1D, Carnitine, analogs and derivs.
577-11-7, Sodium docusate 595-33-5, Megestrol acetate 1622-61-3,
Clonazepam 1972-08-3, Dronabinol 2644-64-6, DPPC 5633-20-5,
Oxybutynin 5786-21-0, Clozapine 5949-44-0, Testosterone undecanoate
9002-96-4 9003-39-8, PVP K30 9004-65-3, Hydroxypropyl methylcellulose
9004-96-0, Crodet O 100 9005-32-7D, Alginic acid, salts 9005-37-2,
Propylene glycol alginate 9005-38-3, Sodium alginate 9005-63-4,
Polyoxyethylene sorbitan 9005-64-5, PEG sorbitan monolaurate
9005-65-6, PEG sorbitan monooleate 9009-32-9, Polyglyceryl stearate
10041-19-7 10238-21-8, Glyburide 10540-29-1, Tamoxifen 11140-04-8,
Imwitor 988 14440-80-3, Stearyl lactylate 18656-38-7, DMPC
21256-18-8, Oxaprozin 25086-15-1, Eudragit L100 25322-68-3,
Polyethylene glycol 25322-68-3D, esters 25618-55-7, Polyglycerol
26545-74-4 27215-38-9, Monomuls 90-45 28721-07-5, Oxacarbazepine
29975-16-4, Estazolam 31566-31-1, Imwitor 191 34911-55-2, Bupropion
37220-82-9, Peceol 47931-85-1, Salmon calcitonin 49562-28-9,
Fenofibrate 51322-75-9, Tizanidine 51333-22-3, Budesonide
53123-88-9, Sirolimus 55142-85-3, Ticlopidine 63675-72-9, Nisoldipine
68475-42-3, Anagrelide 70458-96-7, Norfloxacin 71125-38-7, Meloxicam
72509-76-3, Felodipine 72956-09-3, Carvedilol 73590-58-6, Omeprazole
73963-72-1, Cilostazol 74504-64-6, Polyglyceryl laurate 75330-75-5,
Lovastatin 75695-93-1, Isradipine 77337-76-9, Acamprosate
79902-63-9, Simvastatin 81103-11-9, Clarithromycin 82410-32-0,
Ganciclovir 84057-84-1, Lamotrigine 84449-90-1, Raloxifene
84625-61-6, Itraconazole 87333-19-5, Ramipril 88150-42-9, Amlodipine
91374-21-9, Ropinirole 100427-26-7, Lercanidipine 100986-85-4,
Levofloxacin 103577-45-3, Lansoprazole 104987-11-3, Tacrolimus
106266-06-2, Risperidone 106308-44-5, Rufinamide 106392-12-5,
Oxyethylene-oxypropylene block copolymer 107724-20-9, Eplerenone
107753-78-6, Zafirlukast 111025-46-8, Pioglitazone 112811-59-3,
Gatifloxacin 115103-54-3, Tiagabine 124937-51-5, Tolterodine
127779-20-8, Saquinavir 127829-97-4, Solulan C-24 129318-43-0,
Alendronate sodium 129722-12-9, Aripiprazole 130929-57-6, Entacapone
132539-06-1, Olanzapine 133040-01-4, Eprosartan 134308-13-7, Tolcapone
134523-00-5, Atorvastatin 137862-53-4, Valsartan 139755-83-2,
Sildenafil 145158-71-0, Tegaserod 146478-45-7, Polyglycerol dioleate
146939-27-7, Ziprasidone 147536-97-8, Bosentan 154598-52-4, Efavirenz
156259-68-6, Capmul MCM 162011-90-7, Rofecoxib 169590-42-5, Celecoxib
170729-80-3, Aprepitant 174392-00-8, Polyglyceryl monooleate
197179-53-6, Nonpareil
RL: COS (Cosmetic use); FFD (Food or feed use); THU (Therapeutic use);
BIOL (Biological study); USES (Uses)
(solid carriers for improved delivery of active ingredients contg. surfactants and glycerides)

IT 170729-80-3, Aprepitant
RL: COS (Cosmetic use); FFD (Food or feed use); THU (Therapeutic use);
BIOL (Biological study); USES (Uses)
(solid carriers for improved delivery of active ingredients contg. surfactants and glycerides)

RN 170729-80-3 CAPLUS
CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phen
yl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX

NAME)



Absolute stereochemistry shown
Rotation (+)

OS.CITING REF COUNT: 162 THERE ARE 162 CAPLUS RECORDS THAT CITE THIS RECORD (272 CITINGS)

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
CA 2706113 A1	CA 2000-2706113	Register
JP 2012116863 A	JP 2012-29635	Register|Global Dossier
US 6248363 B1	US 1999-447690	Register
US 20030064097 A1	US 2001-800593	Register
US 6569463 B2	US 2001-800593	Register
US 20030215496 A1	US 2003-428341	Register|Global Dossier
US 6923988 B2	US 2003-428341	Register|Global Dossier
US 20060034937 A1	US 2005-196805	Register|Global Dossier
US 20090074859 A1	US 2008-326711	Register|Global Dossier
US 20140357586 A1	US 2014-14460188	Register|Global Dossier
US 20150224130 A9	US 2014-14460188	Register|Global Dossier
US 20150273067 A1	US 2015-14713692	Register|Global Dossier
US 20180125978 A1	US 2017-15625764	Register|Global Dossier
US 20200061191 A1	US 2019-16289565	Register|Global Dossier
US 20210008212 A1	US 2020-16917731	Register|Global Dossier
WO 2007018943 A2	WO 2006-US27159	Register|Global Dossier
WO 2007018943 A3	WO 2006-US27159	Register|Global Dossier

L4 ANSWER 47 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2005:1311702 CAPLUS Full-text
DOCUMENT NUMBER: 144:57525
TITLE: Coated vaginal devices for vaginal delivery of therapeutically effective and/or health-promoting agents
INVENTOR(S): Wilson, Michelle; Desai, Kishorkumar J.; Pauletti, Giovanni M.; Antoon, Mitchell K.; Clendening, Chris E.
PATENT ASSIGNEE(S): UMD, Inc., USA
ULTIMATE OWNER: U M D
ULTIMATE OWNER STANDARD: U M D
SOURCE: U.S. Pat. Appl. Publ., 40 pp., Cont.-in-part of U.S. Ser. No. 126,863
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 12
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20050276836	A1	20051215	US 2005-180076	20050712
US 6197327	B1	20010306	US 1998-79897	19980515
US 6086909	A	20000711	US 1999-249963	19990212
US 6572874	B1	20030603	US 2000-626025	20000727
NZ 508130	A	20020301	NZ 2000-508130	20001113

AU 2001054192	A	20010913	AU 2001-54192		20010703
AU 765269	B2	20030911			
US 20030049302	A1	20030313	US 2002-226667		20020821
US 6982091	B2	20060103			
US 20040005345	A1	20040108	US 2003-349029		20030122
US 6905701	B2	20050614			
US 20040043071	A1	20040304	US 2003-600849		20030620
US 20050249774	A1	20051110	US 2005-126863		20050510
US 7744916	B2	20100629			
PRIORITY APPLN. INFO.:			US 1997-60049325	P	19970611
			US 1998-79897	A2	19980515
			US 1999-249963	A2	19990212
			US 2000-626025	A2	20000727
			US 2002-226667	A2	20020821
			US 2003-349029	A2	20030122
			US 2003-600849	A2	20030620
			US 2004-60587454	P	20040712
			US 2005-126863	A2	20050510
			AU 1998-76976	A3	19980610
			NZ 1998-502120	A1	19980610
			US 1999-249693	A2	19990212
			US 1999-60146218	P	19990728
			US 2001-60315877	P	20010829
			US 2002-60390748	P	20020621

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
US 20050276836	A1	Dead	20201107
US 6197327	B1	Dead	20201107
US 6086909	A	Dead	20201106
US 6572874	B1	Dead	20201107
NZ 508130	A	Dead	20201121
AU 2001054192	A	Dead	20201107
AU 765269	B2	Dead	20201106
US 20030049302	A1	Dead	20201121
US 6982091	B2	Dead	20201121
US 20040005345	A1	Dead	20201107
US 6905701	B2	Dead	20201107
US 20040043071	A1	Dead	20201121
US 20050249774	A1	Dead	20220310
US 7744916	B2	Dead	20220310

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OTHER SOURCE(S): CASFORMULTNS 2005:1311702

AB Disclosed is a vaginal device for delivering therapeutical and/or health-promoting agents. The vaginal device partly or completely coated by, covered by or combined with a coating or covering comprising a film, foam, strip, cap, cup or particles. The coating of the device comprises a mucoadhesive compn. comprising a therapeutical and/or health-promoting agent. For example, sumatriptan vaginal suppository were prepd. from Suppocire AS2X, hydroxypropyl Me cellulose as a mucoadhesive agent, and Transcutol as a permeation enhancer.

INCL 424422000

IPCI A61F0013-00 [ICM,7]

IPCR A61F0013-00 [I]; A61K0009-00 [I]; A61K0009-02 [I]; A61K0009-12 [I]; A61K0009-19 [I]; A61K0009-70 [I]

NCL 424/422.000

CC 63-6 (Pharmaceuticals)

IT Alkaloids
Amino acids
Bile salts
Cellulosic fibers
Coenzymes
Cottonseed oil
Essential oils
Fats and Glyceridic oils
Interleukins
Lecithins
Minerals
Natural products, pharmaceutical
Peptides
Phenols
Polyketides

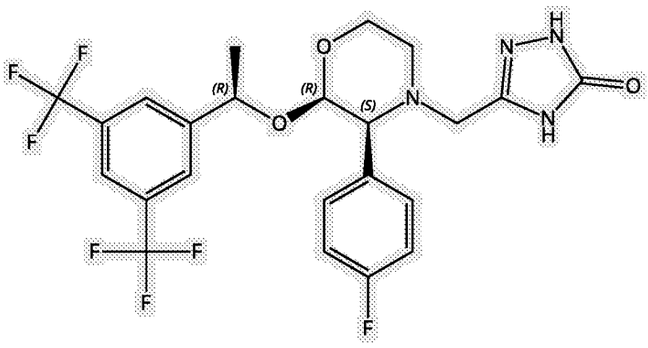
Polyoxyalkylenes
Proteins
Resins
Silicone rubber
Tannins
Terpenes
Vitamins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(coated vaginal devices for vaginal delivery of therapeutically effective and/or health-promoting agents)

IT 68379-02-2, Clofilium 69655-05-6, Didanosine 70458-96-7, Norfloxacin 71048-87-8, Levonantradol 71125-38-7, Meloxicam 72479-26-6, Fenticonazole 72509-76-3, Felodipine 73573-87-2, Formoterol 74103-06-3, Ketorolac 74103-07-4, Ketorolac tromethamine 74191-85-8, Doxazosin 74545-79-2, Aloeresin A 75088-80-1, Manoalide 75330-75-5, Lovastatin 75695-93-1, Isradipine 76584-70-8, Divalproex sodium 79350-37-1, Cefixime 79778-41-9, Neridronate 80210-62-4, Cefpodoxime 80937-31-1, Flosulide 82410-32-0, Ganciclovir 83905-01-5, Azithromycin 83991-25-7, Ambasilide 84625-61-6, Itraconazole 85622-93-1, Temozolomide 85721-33-1, Ciprofloxacin 86386-73-4, Fluconazole 88150-42-9, Amlodipine 89365-50-4, Salmeterol 89565-68-4, Tropisetron 89778-26-7, Toremifene 89987-06-4, Tiludronate 90357-06-5, Bicalutamide 90961-53-8, Tedisamil 91714-94-2, Bromfenac 92665-29-7, Cefprozil 95058-81-4, Gemcitabine 95298-47-8 95751-30-7, Charybdotoxin 97240-79-4, Topiramate 97682-44-5, Irinotecan 98079-51-7, Lomefloxacin 98225-48-0, Brevetoxin 99614-02-5, Ondansetron 101526-83-4, Sematilide 103628-46-2, Sumatriptan 104227-87-4, Famciclovir 105462-24-6 107868-30-4, Exemestane 110042-95-0, Acemannan 112455-84-2, Papuamine 112809-51-5, Letrozole 114084-78-5, Ibandronate 114977-28-5, Docetaxel 115256-11-6, Dofetilide 115956-12-2, Dolasetron 118072-93-8, Zoledronate 120511-73-1, Anastrozole 121368-58-9, Olpadronate 121679-13-8, Naratriptan 122647-31-8, Ibutilide 123948-87-8, Topotecan 127779-20-8, Saquinavir 129618-40-2, Nevirapine 132539-06-1, Olanzapine 134678-17-4, Lamivudine 135729-61-2, Palonosetron 136470-78-5, Abacavir 136817-59-9, Delavirdine 137234-62-9, Voriconazole 139110-80-8, Zanamivir 139226-28-1, Darbufelone 139264-17-8, Zolmitriptan 143322-58-1, Eletriptan 143491-57-0, Emtricitabine 144034-80-0, Rizatriptan 147127-20-6, Tenofovir 149908-53-2, Azimilide 150378-17-9, Indinavir 152459-95-5, Imatinib 153559-49-0, Bexarotene 154323-57-6, Almotriptan 154361-50-9, Capecitabine 154598-52-4, Efavirenz 155213-67-5, Ritonavir 158751-64-5, ClAmikalant 159519-65-0, Enfuvirtide 159989-64-7, Nelfinavir 161814-49-9, Amprenavir 162011-90-7, Rofecoxib 169590-42-5, Celecoxib 169944-35-8, Bisulfan 170729-80-3, Aprepitant 181695-72-7, Valdecoxib 184475-35-2, Gefitinib 190017-00-6, Correolide 192725-17-0, Lopinavir 196618-13-0, Oseltamivir 198470-84-7, Parecoxib 198904-31-3, Atazanavir 202409-33-4, Etoricoxib 220991-20-8, Lumiracoxib 226700-79-4, Fosamprenavir 260792-29-8, 6β,7β-Diacetoxy-13-hydroxylabda-8,14-diene 264875-61-8, Cimiracemoside A 501938-01-8, 23-epi-26-Deoxyactein 856012-03-8 865111-98-4 865147-59-7, Altissinone 871260-93-4
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(coated vaginal devices for vaginal delivery of therapeutically effective and/or health-promoting agents)

IT 170729-80-3, Aprepitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(coated vaginal devices for vaginal delivery of therapeutically effective and/or health-promoting agents)

RN 170729-80-3 CAPLUS

CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

OS.CITING REF COUNT: 23 THERE ARE 23 CAPLUS RECORDS THAT CITE THIS RECORD (23 CITINGS)

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
AU 2001054192 A	AU 2001-54192	Register
AU 765269 B2	AU 2001-54192	Register
NZ 508130 A	NZ 2000-508130	Register
US 6197327 B1	US 1998-79897	Register
US 6086909 A	US 1999-249963	Register
US 6572874 B1	US 2000-626025	Register
US 20030049302 A1	US 2002-226667	Register
US 6982091 B2	US 2002-226667	Register
US 20040005345 A1	US 2003-349029	Register|Global Dossier
US 6905701 B2	US 2003-349029	Register|Global Dossier
US 20040043071 A1	US 2003-600849	Register|Global Dossier
US 20050249774 A1	US 2005-126863	Register|Global Dossier
US 7744916 B2	US 2005-126863	Register|Global Dossier
US 20050276836 A1	US 2005-180076	Register|Global Dossier

L4 ANSWER 48 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2002:695760 CAPLUS Full-text
DOCUMENT NUMBER: 137:237717
TITLE: Inhalant compositions containing anticholinergics and NK1 receptor antagonists
INVENTOR(S): Meade, Christopher John Montague; Pairet, Michel; Pieper, Michael Paul
PATENT ASSIGNEE(S): Boehringer Ingelheim Pharma K.-G., Germany
SOURCE: PCT Int. Appl., 42 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 14
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002069944	A2	20020912	WO 2002-EP1987	20020226
WO 2002069944	A3	20031002		
DE 10111058	A1	20020912	DE 2001-10111058	20010308
CA 2439915	A1	20020912	CA 2002-2439915	20020226
AU 2002251010	A1	20020919	AU 2002-251010	20020226
EP 1370293	A2	20031217	EP 2002-719915	20020226
JP 2004519484	T	20040702	JP 2002-569121	20020226
MX 2003008051	A	20031204	MX 2003-8051	20030905

PRIORITY APPLN. INFO.:
DE 2001-10111058 A 20010308
WO 2002-EP1987 W 20020226

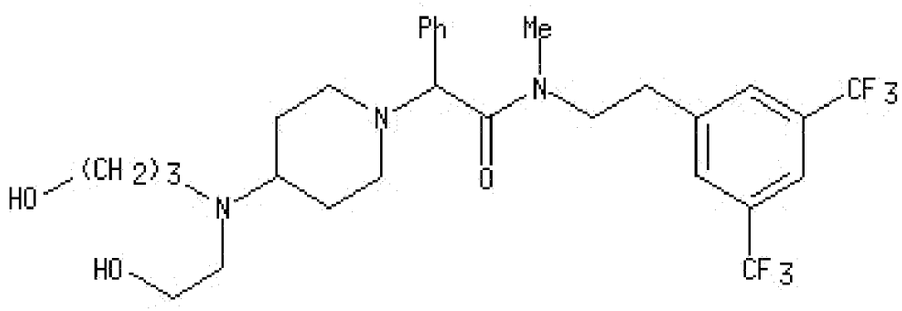
PATENT STATUS PATENT INFORMATION:

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WO 2002069944	A3	Dead	20201201
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CA 2439915	A1	Dead	20201121
AU 2002251010	A1	Dead	20201121
EP 1370293	A2	Dead	20201202
JP 2004519484	T	Dead	20220303
MX 2003008051	A	Dead	20201121

OTHER SOURCE(S): MARPAT 137:237717; CASFORMULTNS 2002:695760

GI



AB The invention relates to drug compns. based on anticholinergics and on NK1 receptor antagonists, to methods for their prodn., and to their use as inhalants for the treatment of respiratory tract diseases. Synthesis of NK1 receptor antagonists from the group of bis-trifluoromethyl-phenyl-piperidine derivs. are described. The products are used in suspension aerosols. Thus a compn. contained (wt./wt.%): tiotropium bromide 0.015; NK1 receptor antagonist 0.066; soy lecithin 0.2; TG11: TG12 = 2:3 to 100.

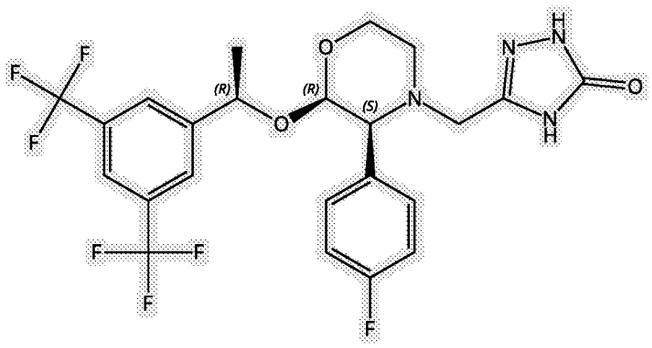
IPCI A61K0031-00 [ICM,7]

IPCR A61K0009-08 [I]; A61K0009-00 [I]; A61K0009-10 [I]; A61K0009-14 [I]; A61K0009-48 [I]; A61K0009-72 [I]; A61K0031-00 [I]; A61K0031-223 [I]; A61K0031-403 [I]; A61K0031-439 [I]; A61K0031-4468 [I]; A61K0031-46 [I]; A61K0031-4745 [I]; A61K0031-535 [I]; A61K0031-55 [I]; A61K0045-06 [I]; A61K0047-04 [I]; A61K0047-10 [I]; A61K0047-12 [I]; A61K0047-18 [I]; A61K0047-22 [I]; A61K0047-26 [I]; A61P0011-00 [I]; A61P0011-08 [I]; A61P0029-00 [I]; A61P0043-00 [I]

CC 63-6 (Pharmaceuticals)

IT 50-81-7, Ascorbic acid, biological studies 56-81-5, Glycerol, biological studies 57-55-6, Propylene glycol, biological studies 64-02-8 64-17-5, Ethanol, biological studies 64-18-6, Formic acid, biological studies 64-19-7, Acetic acid, biological studies 65-85-0, Benzoic acid, biological studies 74-98-6, n-Propane, biological studies 75-28-5, Isobutane 77-92-9, Citric acid, biological studies 79-09-4, Propionic acid, biological studies 106-97-8, n-Butane, biological studies 110-15-6, Succinic acid, biological studies 110-16-7, Maleic acid, biological studies 110-17-8, Fumaric acid, biological studies 123-03-5, Cetylpyridinium chloride 431-89-0, TG227 526-83-0, Tartaric acid 811-97-2, TG134a 1406-18-4, Vitamin E 6915-15-7, Malic acid 7647-01-0, Hydrochloric acid, biological studies 7664-93-9, Sulfuric acid, biological studies 7697-37-2, Nitric acid, biological studies 10035-10-6, Hydrobromic acid, biological studies 11103-57-4, Vitamin A 25322-68-3, Polyethylene glycol 25322-68-3D, alcs. and fatty acid esters 25322-69-4, Polypropylene glycol 60205-81-4, Ipratropium 99571-64-9, Oxitropium 138449-07-7, FK-888 142001-63-6, Saredutant 145742-28-5, CP-122721 147116-64-1, CJ 11974 155418-05-6, SR 140333 168266-90-8, GR 205171 170566-84-4, Lanepitant 170739-80-3, MK-869 171272-39-2, MEN-10930 172673-20-0, L-758298 173941-19-0, YM 49244 173941-22-5, YM 35375 173941-74-7, YM 44778 174636-32-9, SB 223412 174661-97-3, DA-5018 178370-50-8, MDL 103896 183747-35-5, Nepadutant 188241-50-1, S-19752 193694-35-8, MDL-105172A 201152-86-5, SR-144190 206052-25-7, MEN-11149 209474-01-1, Neuronorm 214487-46-4, MEN-11467 217185-75-6, TAK-637 350610-25-2 350610-26-3, 6b-I 350610-27-4, DNK-33A 350610-29-6, ZM-274773 350610-34-3, DNK 333A 350610-51-4, CGP 60829 350610-61-6, NKP 608A 350610-64-9, NKP 608C 415917-13-4 457910-81-5 458568-84-8, TG 11 458569-01-2, TG 12
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(inhalant compns. contg. anticholinergics and NK1 receptor antagonists)
IT 170729-80-3, MK-869
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhalant compns. contg. anticholinergics and NK1 receptor antagonists)
RN 170729-80-3 CAPLUS
CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

OS.CITING REF COUNT: 4 THERE ARE 4 CAPLUS RECORDS THAT CITE THIS RECORD (4 CITINGS)
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
AU 2002251010 A1	AU 2002-251010	Register
CA 2439915 A1	CA 2002-2439915	Register
DE 10111058 A1	DE 2001-10111058	Register
EP 1370293 A2	EP 2002-719915	Register|Federated Reg.
JP 2004519484 T	JP 2002-569121	Register
MX 2003008051 A	MX 2003-8051	Register
WO 2002069944 A2	WO 2002-EP1987	Register|Global Dossier
WO 2002069944 A3	WO 2002-EP1987	Register|Global Dossier

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FULL ESTIMATED COST                                 0.35             0.35

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DICTIONARY FILE UPDATES:   2 JUN 2024  HIGHEST RN 3038107-58-0

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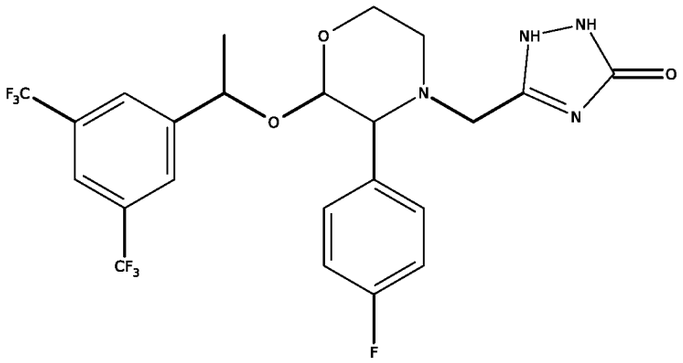
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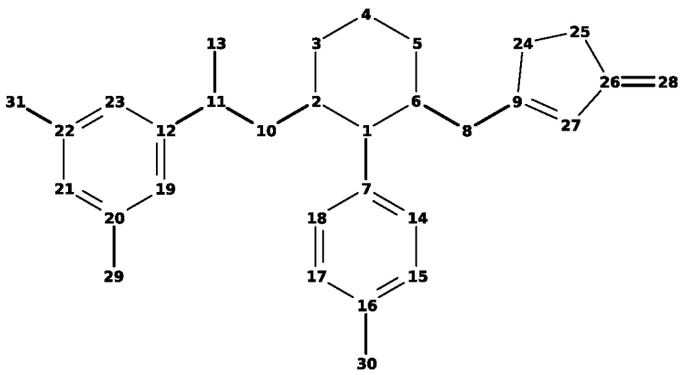
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Chain Nodes : 8 10 11 13 28 30
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SAMPLE SCREEN SEARCH COMPLETED -       53 TO ITERATE

100.0% PROCESSED         53 ITERATIONS                                5 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:          624 TO     1496
PROJECTED ANSWERS:               5 TO      234

L2            5 SEA SSS SAM L1

=> S L1 SSS FULL

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FULL SCREEN SEARCH COMPLETED -      805 TO ITERATE

100.0% PROCESSED        805 ITERATIONS                               68 ANSWERS
SEARCH TIME: 00.00.01

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=> FILE CAPLUS

COST IN U.S. DOLLARS                          SINCE FILE            TOTAL
                                                   ENTRY          SESSION
FULL ESTIMATED COST                               889.79           890.14

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FILE LAST UPDATED: 2 Jun 2024 (20240602/ED)

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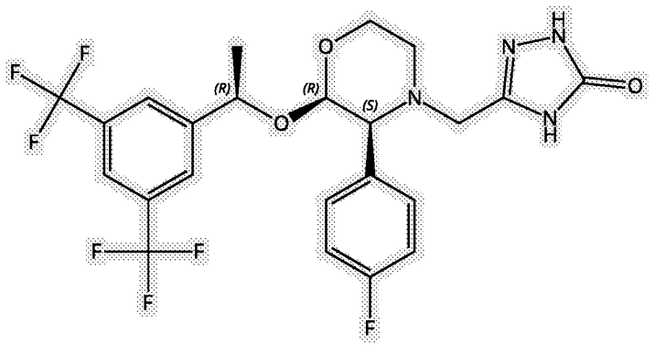
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          62827 LECITHINS
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                (LECITHIN OR LECITHINS)
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L5   ANSWER 1 OF 48  CAPLUS  COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER:         2024:141628  CAPLUS Full-text
TITLE:                    Aprepitant emulsion drug composition and preparation
                          method thereof
INVENTOR(S):              Chen, Xiangmei; Yu, Changhui; Wang, Xinlong; Lin,
                          Liyang; Shen, Li; Zhao, Dong
PATENT ASSIGNEE(S):       Sichuan Kelun Pharmaceutical Research Institute Co.,
                          Ltd., Peop. Rep. China
ULTIMATE OWNER:           SICHUAN KELUN PHARMACEUTICAL COMPANY LIMITED
ULTIMATE OWNER STANDARD: Sichuan KELUN
SOURCE:                   Faming Zhuanli Shenqing, 8pp.
                          CODEN: CNXXEV
DOCUMENT TYPE:            Patent
LANGUAGE:                 Chinese
FAMILY ACC. NUM. COUNT:   1
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PATENT STATUS PATENT INFORMATION:
     PATENT NO.           KIND  STATUS          STATUS DATE
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AB   The present invention provides an aprepitant emulsion drug compn. and
     prepn. method thereof, which has the advantages of high quality and good
     stability.  The method comprises the following steps: stirring and
     dissolving aprepitant, phospholipid, ethanol and soybean oil to obtain an
     oil phase, adding an isotonic regulator, the phospholipid and a pH
     regulator into water for injection, stirring uniformly to obtain a water
     phase, online shearing and mixing the oil phase and the water phase to
     prep. a primary emulsion, homogenizing by high-pressure microjet,
     sterilizing, filtering and filling.
IPCI A61K0009-107; A61K0031-5377; A61K0047-24; A61K0047-44; A61P0001-08
IPCR A61K0009-107 [I]; A61K0031-5377 [I]; A61K0047-24 [I]; A61K0047-44 [I];
     A61P0001-08 [I]
CC   63 (Pharmaceuticals)
IT   INDEXING IN PROGRESS
IT   Egg yolk lecithins
     Soybean oil
     RL: MOA (Modifier or additive use); PEP (Physical, engineering or chemical
     process); THU (Therapeutic use); BIOL (Biological study); PROC (Process);
     USES (Uses)
        (aprepitant emulsion drug compn. and prepn. method thereof)
IT   170729-80-3, Aprepitant
     RL: PEP (Physical, engineering or chemical process); THU (Therapeutic
     use); BIOL (Biological study); PROC (Process); USES (Uses)
        (aprepitant emulsion drug compn. and prepn. method thereof)
IT   170729-80-3, Aprepitant
     RL: PEP (Physical, engineering or chemical process); THU (Therapeutic
     use); BIOL (Biological study); PROC (Process); USES (Uses)
        (aprepitant emulsion drug compn. and prepn. method thereof)
RN   170729-80-3  CAPLUS
CN   3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phen
yl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro-  (CA INDEX
NAME)
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Absolute stereochemistry shown
Rotation (+)

LINK INFORMATION

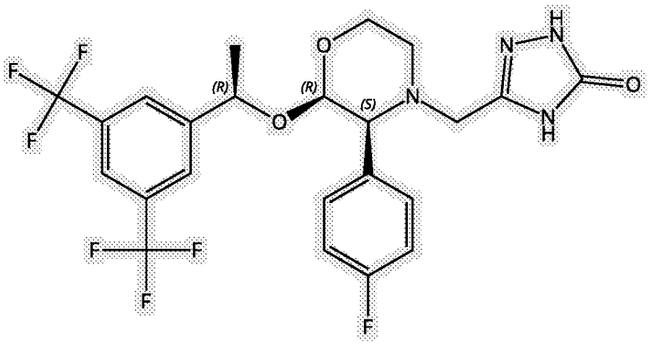
PUBLICATIONS	APPLICATIONS	REGISTER
CN 117414334 A	CN 2022-10811953	Register|Global Dossier

L5 ANSWER 2 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2023:1752935 CAPLUS Full-text
DOCUMENT NUMBER: 184:181224
TITLE: Formulation and evaluation of lipid nanoparticulate drug delivery system of Aprepitant for the treatment of Cinv
AUTHOR(S): R., Joan Vijetha; Balamurugan, K.
CORPORATE SOURCE: College of Pharmacy, Sathyabama Institute of Science and Technology, Semmancheri, Chennai, 600119, India
SOURCE: Journal of Pharmaceutical Negative Results (2022), 13(Spec.Iss.10), 5114-5127
CODEN: JPNRBH; ISSN: 2229-7723
URL: https://www.pnrjournal.com/index.php/home/index
DIGITAL OBJECT ID: 10.47750/pnr.2022.13.s10.627
PUBLISHER: ResearchTrentz
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English

AB The present study was to formulate and evaluate the Aprepitant USP is a substance P/neurokinin 1 (NK1) receptor antagonist as nanoparticulate lipid carriers (AP-NLC) drug delivery systems and comparing with the marketed product. The formulations of AP-NLC were prepd. by the homogenization followed by ultrasonication method using the solid lipid as Glyceryl behenate, the liq. lipid Caprylocaproyl polyoxyglycerides and polysorbate 80 as hydrophilic surfactant. Based on the trial expts., the compn. of optimized formulation was AP-NLC blend consist of 125 mg of Aprepitant, 210 mg Glyceryl behenate, 90 mg Caprylocaproyl polyoxyglycerides, 36 mg polysorbate 80 and 20 mg soya lecithin. By liquisolid technique mesoporous silica gel taken was 160.4 mg was mixed with above AP-NLC blend to form from the optimized AP-NLC12 capsules. The AP NLC12 was found to be with mean particle size of mean av. of 200.6 nm with max. intensity of 541.0 nm particles, The dissoln. data demonstrates that the drug release was increased by 5-12% increase in drug release in initial time points upto 3 h as compared to the marketed product and the release is sustained up to 30 h as compared to the 10 h for the marketed product. The drug release kinetics of AP NLC 12 was by Korsmeyer-Peppas model confirms the drug release from a polymeric system and release mechanisms was diffusion followed by erosion.This research is an attempt was made to design Aprepitant USP nanoparticulate lipid carrier drug delivery systems for sustained drug release in treatment chemotherapy induced nausea and vomiting (CINV).

CC 63-6 (Pharmaceuticals)
IT Soya lecithins
RL: NANO (Nanomaterial); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(formulation and evaluation of lipid nanoparticulate drug delivery

system of aprepitant for treatment of chemotherapy induced nausea and vomiting)
IT 9005-65-6 18641-57-1 170729-80-3
RL: NANO (Nanomaterial); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(formulation and evaluation of lipid nanoparticulate drug delivery system of aprepitant for treatment of chemotherapy induced nausea and vomiting)
IT 170729-80-3
RL: NANO (Nanomaterial); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(formulation and evaluation of lipid nanoparticulate drug delivery system of aprepitant for treatment of chemotherapy induced nausea and vomiting)
RN 170729-80-3 CAPLUS
CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 3 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2023:1213332 CAPLUS Full-text
DOCUMENT NUMBER: 183:142125
TITLE: Personalized starvation therapy for cancer by administering an inhibitor of the mevalonate pathway with a diet low in cholesterol or lipids
INVENTOR(S): Maddocks, Oliver D. K.; Mishra, Swati
PATENT ASSIGNEE(S): Faeth Therapeutics, Inc., USA
ULTIMATE OWNER: FAETH THERAPEUTICS INC
ULTIMATE OWNER STANDARD: FAETH THERAPEUTICS INC
SOURCE: PCT Int. Appl., 210pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2023108146	A1	20230615	WO 2022-US81307		20221209
PRIORITY APPLN. INFO.:			US 2021-63288062	P	20211210

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
WO 2023108146	A1	Alive	20230629

AB Disclosed herein are methods of administering an inhibitor of the mevalonate pathway with a diet low in cholesterol or lipids. The methods of the present invention can be used to treat conditions such as cancer.
IPCI A61K0031-33 [I]; A61K0031-045 [I]; A61K0031-395 [I]; A61K0031-01 [N]
IPCR A61K0031-33 [I]; A61K0031-01 [N]; A61K0031-045 [I]; A61K0031-395 [I]

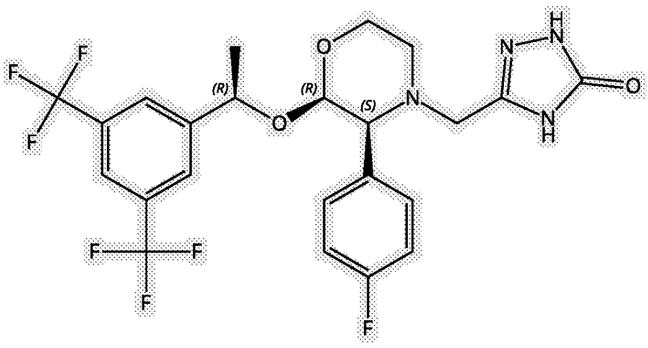
CC 1-6 (Pharmacology)
Section cross-reference(s): 18, 63
IT Castor oil
Lanolin
Lecithins
Tannins
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(personalized starvation therapy for cancer by administering an inhibitor of mevalonate pathway with a diet low in cholesterol or lipids and combination with other agents)
IT 9031-14-5, Lecithin-cholesterol acyltransferase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; personalized starvation therapy for cancer by administering an inhibitor of mevalonate pathway with a diet low in cholesterol or lipids and combination with other agents)
IT 118292-40-3, Tazarotene 119169-78-7, Epristeride 119302-91-9, Rocuronium (Bromide) 119413-54-6, Topotecan (Hydrochloride) 119478-55-6, Danofloxacin (mesylate) 119478-56-7, Meropenem (trihydrate) 119615-63-3, Olprinone (Hydrochloride) 119637-67-1, Moguisteine 119793-66-7, Levocarnitine propionate (hydrochloride) 120011-70-3, Donepezil (Hydrochloride) 120014-06-4, Donepezil 120068-37-3, Fipronil 120202-66-6, Clopidogrel (hydrogen sulfate) 120410-24-4, Biapenem 120511-73-1, Anastrozole 120638-55-3 120685-11-2, Midostaurin 120876-23-5 121032-29-9, Nelarabine 121123-17-9, Cefprozil (monohydrate) 121268-17-5 121808-62-6, Pidotimod 122111-03-9, Gemcitabine (hydrochloride) 122320-73-4, Rosiglitazone 122341-38-2, Temoporfin 122547-49-3, Faropenem sodium 122647-32-9, Ibutilide (fumarate) 122841-12-7, Cefoselis (sulfate) 122852-69-1, Alosetron (Hydrochloride) 122892-31-3, Itopride (hydrochloride) 123040-16-4, Azasetron hydrochloride 123171-59-5, Cefepime (Dihydrochloride Monohydrate) 123318-82-1, Clofarabine 123441-03-2, Rivastigmine 123447-62-1, Prulifloxacin 123524-52-7, Azelnidipine 123663-49-0, Iguratimod 124750-99-8, Losartan (potassium) 124832-27-5, Valacyclovir (hydrochloride) 124858-35-1, Nadifloxacin 124937-51-5, Tolterodine 124937-52-6, Tolterodine (tartrate) 125572-93-2, Rotigotine (Hydrochloride) 125602-71-3, Bepotastine 126544-47-6, Ciclesonide 126784-99-4, Ulipristal acetate 127373-66-4, Sivelestat 127779-20-8, Saquinavir 127984-74-1, Lanreotide (acetate) 128607-22-7, Ospemifene 128794-94-5, Mycophenolate Mofetil 129101-54-8, Rivastigmine (tartrate) 129453-61-8, Fulvestrant 129497-78-5, Verteporfin 129618-40-2, Nevirapine 129722-12-9, Aripiprazole 129938-20-1, Dapoxetine (hydrochloride) 130018-87-0, Levocetirizine (dihydrochloride) 130209-82-4, Latanoprost 130693-82-2, Dorzolamide (hydrochloride) 130726-68-0, Neticonazole 130773-02-3, Neticonazole (hydrochloride) 130929-57-6, Entacapone 131410-48-5, Gadodiamide 131707-23-8, Umifenovir (hydrochloride) 132112-35-7, Ropivacaine (hydrochloride monohydrate) 132203-70-4, Cilnidipine 132539-06-1, Olanzapine 132810-10-7, Blonanserin 132866-11-6, Lercanidipine (hydrochloride) 132907-72-3, Ramosetron (Hydrochloride) 133033-93-9, (±)-Darifenacin 133099-07-7, Darifenacin (hydrobromide) 133454-47-4, Iloperidone 133865-89-1 134308-13-7, Tolcapone 134418-28-3, Dehydroandrographolide 134523-00-5, Atorvastatin 134523-03-8, Atorvastatin calcium 134678-17-4, Lamivudine 135062-02-1, Repaglinide 135159-51-2, Sarpogrelate (hydrochloride) 135326-22-6, Gadoxetate (Disodium) 135729-62-3, Palonosetron (Hydrochloride) 136087-85-9, Fidarestat 136310-93-5, Tiotropium (Bromide) 136434-34-9, Duloxetine (hydrochloride) 136470-78-5, Abacavir 136572-09-3, Irinotecan (hydrochloride trihydrate) 137071-32-0, Pimecrolimus 137234-62-9, Voriconazole 137281-23-3, Pemetrexed 137862-53-4, Valsartan 137975-06-5, Mozavaptan 138112-76-2, Agomelatine 138402-11-6, Irbesartan 138470-70-9, Mozavaptan (hydrochloride) 138530-94-6, (R)-Lansoprazole 138614-30-9, Icatibant (acetate) 138786-67-1, Pantoprazole (sodium) 138890-62-7, Brinzolamide 138926-19-9, Ibandronate (Sodium Monohydrate) 138982-67-9, Ziprasidone (hydrochloride monohydrate) 139110-80-8, Zanamivir 139481-59-7, Candesartan 139755-83-2, Sildenafil 139755-85-4, Lodenafil 140462-76-6, Olopatadine (hydrochloride) 140678-14-4, Mangafodipir (trisodium) 140898-91-5, Hexaminolevulinate (hydrochloride) 141396-28-3, Argatroban (monohydrate) 141433-60-5, Berberine (chloride hydrate) 141505-33-1, Levosimendan 141625-93-6, Dronedarone (Hydrochloride) 141626-36-0, Dronedarone 141702-36-5, Faropenem daloxate 142128-59-4,

(+)-Ketoconazole 142340-99-6, Adefovir dipivoxil 143388-64-1, Naratriptan (hydrochloride) 143491-57-0, Emtricitabine 144060-53-7, Febuxostat 144143-96-4, Eprosartan (mesylate) 144481-98-1, Landiolol (hydrochloride) 144598-75-4, Paliperidone 144675-97-8, Pixantrone (dimaleate) 144689-24-7, Olmesartan 144689-63-4, Olmesartan medoxomil 144701-48-4, Telmisartan 145040-37-5, Candesartan Cilexetil 145108-58-3, Dexmedetomidine (hydrochloride) 145202-66-0, Rizatriptan (benzoate) 145435-72-9, Gamithromycin 145525-41-3, Mitiglinide (Calcium) 145672-81-7, Cetrorelix (Acetate) 145781-92-6, Goserelin (acetate) 145821-59-6, Tiagabine (hydrochloride) 146464-95-1, Pralatrexate 146939-27-7, Ziprasidone 147059-72-1, Trovafloxacin 147084-10-4, Alcaftadine 147098-20-2, Rosuvastatin calcium 147127-20-6, Tenofovir 147221-93-0, Delavirdine (mesylate) 147403-03-0, Azilsartan 147511-69-1, Pitavastatin 147526-32-7, Pitavastatin calcium 147536-97-8, Bosentan 148408-66-6, Docetaxel (Trihydrate) 148849-67-6, Ivabradine (hydrochloride) 149003-01-0, Dexrazoxane (hydrochloride) 149647-78-9, Vorinostat 149709-62-6, Sacubitril 149845-06-7, Saquinavir (Mesylate) 150322-43-3, Prasugrel 150399-23-8, Pemetrexed (disodium) 150566-71-5, Levamlodipine besylate 150683-30-0, Tolvaptan 150821-03-7, Pranlukast (hemihydrate) 150915-40-5, Tirofiban (hydrochloride monohydrate) 150915-41-6, Perospirone 151767-02-1, Montelukast (sodium) 152459-95-5, Imatinib 152520-56-4, Nebivolol (hydrochloride) 152658-17-8, Nalfurafine (hydrochloride) 153439-40-8, Fexofenadine (hydrochloride) 153504-70-2, Cevimeline (hydrochloride hemihydrate) 153559-49-0, Bexarotene 154229-18-2, Abiraterone acetate 154229-19-3, Abiraterone 154361-50-9, Capecitabine 154598-52-4, Efavirenz 155141-29-0, Rosiglitazone (maleate) 155148-31-5, Plerixafor (octahydrochloride) 155206-00-1, Bimatoprost 155213-67-5, Ritonavir 155270-99-8, Istradefylline 155558-32-0, Hydroxyfasudil (hydrochloride) 155569-91-8, Emamectin (Benzoate) 156137-99-4, Rapacuronium bromide 157212-55-0, Bosentan (hydrate) 157283-68-6, Travoprost 157810-81-6, Indinavir (sulfate) 158681-13-1, Rimonabant (Hydrochloride) 158930-17-7, Frovatriptan succinate hydrate 159351-69-6, Everolimus 159989-64-7, Nelfinavir 159989-65-8, Nelfinavir (Mesylate) 160970-54-7, Silodosin 161715-24-8, Tebipenem pivoxil 161735-79-1, Rasagiline (mesylate) 161804-20-2 161814-49-9, Amprenavir 161973-10-0, Esomeprazole magnesium 162011-90-7, Rofecoxib 162359-55-9, Fingolimod 162359-56-0, Fingolimod (hydrochloride) 162401-32-3, Roflumilast 162635-04-3, Temsirolimus 163222-33-1, Ezetimibe 163252-36-6, Clevudine 163253-37-0 163451-81-8, Teriflunomide 163521-08-2, Vilazodone (Hydrochloride) 163521-12-8, Vilazodone 163521-19-5 163680-77-1, Pazufloxacin (mesylate) 163706-36-3, Cangrelor (tetrasodium) 164650-44-6, Efinaconazole 164656-23-9, Dutasteride 165800-03-3, Linezolid 165800-06-6, Zoledronic acid (monohydrate) 166663-25-8, Anidulafungin 166734-83-4 167221-71-8, Clevidipine 167933-07-5, Flibanserin 168626-94-6, Conivaptan (hydrochloride) 169590-41-4, Deracoxib 169590-42-5, Celecoxib 170098-38-1, Alvimopan (dihydrate) 170105-16-5, Imidafenacin 170729-80-3, Aprepitant 171228-49-2, Posaconazole 171596-29-5, Tadalafil 171599-83-0, Sildenafil (citrate) 172152-36-2, Ilaprazole 172152-50-0, Ilaprazole (sodium) 173334-57-1, Aliskiren 173334-58-2, Aliskiren (hemifumarate) 173352-39-1 174484-41-4, Tipranavir 174671-46-6, Tavaborole 175865-59-5, Valganciclovir (hydrochloride) 177036-94-1, Ambrisentan 177834-92-3, Eletriptan (hydrobromide) 178307-42-1, Revaprazan (hydrochloride)
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(personalized starvation therapy for cancer by administering an inhibitor of mevalonate pathway with a diet low in cholesterol or lipids and combination with other agents)

IT 170729-80-3, Aprepitant
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(personalized starvation therapy for cancer by administering an inhibitor of mevalonate pathway with a diet low in cholesterol or lipids and combination with other agents)

RN 170729-80-3 CAPLUS

CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
WO 2023108146 A1	WO 2022-US81307	Register|Global Dossier

L5 ANSWER 4 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2022:2496852 CAPLUS Full-text
DOCUMENT NUMBER: 180:210930
TITLE: Compositions having improved bioavailability of therapeutics
INVENTOR(S): Brew, John; Gooding, Daniel; Bannister, Robin M.
PATENT ASSIGNEE(S): TRx Biosciences Limited, UK
ULTIMATE OWNER: TRX BIOSCIENCES
ULTIMATE OWNER STANDARD: TRX BIOSCIENCES
SOURCE: U.S. Pat. Appl. Publ., 202pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20220305125	A1	20220929	US 2022-17656702	20220328
CA 3212583	A1	20221006	CA 2022-3212583	20220328
WO 2022207580	A2	20221006	WO 2022-EP58180	20220328
WO 2022207580	A3	20221229		
AU 2022248850	A1	20231109	AU 2022-248850	20220328
EP 4312978	A2	20240207	EP 2022-718916	20220328
KR 2024021751	A	20240219	KR 2023-7037012	20220328
JP 2024511208	T	20240312	JP 2023-559684	20220328
WO 2023174948	A2	20230921	WO 2023-EP56506	20230314
WO 2023174948	A3	20231026		
US 20240075147	A1	20240307	US 2023-18487486	20231016
IN 202347072261	A	20231215	IN 2023-47072261	20231023

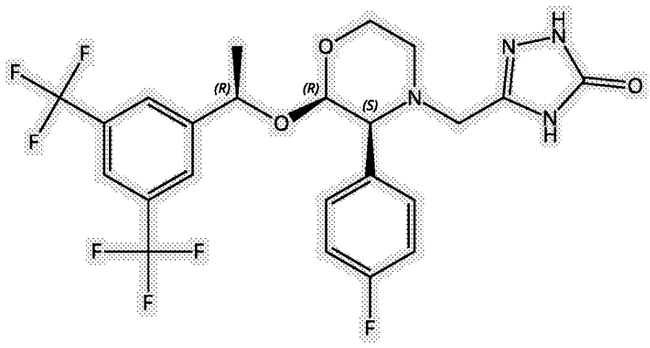
PRIORITY APPLN. INFO.:

US 2021-63166995	P	20210327
US 2022-63269330	P	20220314
US 2022-17656702	A1	20220328
WO 2022-EP58180	W	20220328

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
US 20220305125	A1	Alive	20221006
CA 3212583	A1	Alive	20231005
WO 2022207580	A2	Alive	20221013
WO 2022207580	A3	Alive	20230112
AU 2022248850	A1	Alive	20231116
EP 4312978	A2	Alive	20240208
KR 2024021751	A	Alive	20240314

JP 2024511208 T Alive 20240321
WO 2023174948 A2 Alive 20230928
US 20240075147 A1 Alive 20240314
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASFORMULTNS 2022:2496852
AB The present specification discloses pharmaceutical compn. disclosed herein comprises one or more therapeutic compds., one or more glycerolipids, and one or more digestion enhancers. The disclosed glycerolipids comprise one or more hard fats and one or more liq. fats. The disclosed digestion enhancers comprise one or more bile acids, one or more phospholipids, one or more free C14-24 fatty acids, one or more free C14-24 fatty acid surfactants, or any combination thereof. The present specification also discloses methods and procedures to formulate the disclosed one or more therapeutic compds. into the disclosed pharmaceutical compns.
IPCI A61K0047-14 [I]; A61K0047-28 [I]; A61K0031-12 [I]; A61K0031-216 [I]; A61K0031-05 [I]; A61K0031-58 [I]; A61K0031-7135 [I]; A61K0031-192 [I]; A61K0031-553 [I]; A61K0031-4418 [I]; A61K0031-4453 [I]; A61K0031-196 [I]; A61K0031-44 [I]; A61K0031-4184 [I]; A61K0031-436 [I]; A61K0031-5377 [I]; A61K0031-502 [I]; A61K0031-496 [I]; A61K0031-4025 [I]; A61K0038-12 [I]
IPCR A61K0047-14 [I]; A61K0031-05 [I]; A61K0031-12 [I]; A61K0031-192 [I]; A61K0031-196 [I]; A61K0031-216 [I]; A61K0031-4025 [I]; A61K0031-4184 [I]; A61K0031-436 [I]; A61K0031-44 [I]; A61K0031-4418 [I]; A61K0031-4453 [I]; A61K0031-496 [I]; A61K0031-502 [I]; A61K0031-5377 [I]; A61K0031-553 [I]; A61K0031-58 [I]; A61K0031-7135 [I]; A61K0038-12 [I]; A61K0047-28 [I]
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1
IT Bile acids
Fats and Glyceridic oils
Fatty acids
Glycerolipids
Lecithins
Monoglycerides
Phospholipids
Polyoxyalkylenes
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. having improved bioavailability of therapeutics)
IT 458-37-7, Curcumin 4394-00-7, Niflumic acid 15307-79-6, Diclofenac sodium 15307-86-5, Diclofenac 15687-27-1, Ibuprofen 22204-53-1, Naproxen 31121-93-4 31431-39-7, Mebendazole 34031-32-8, Auranofin 53179-13-8, Pirfenidone 68302-57-8, Amlexanox 88170-10-9, Diclofenac calcium 120685-11-2, Midostaurin 130308-48-4, Icatibant 144701-48-4, Telmisartan 154229-19-3, Abiraterone 170729-80-3, Aprepitant 362665-56-3, Pitolisant 491833-29-5, Eliglustat 656247-17-5, Nintedanib 763113-22-0, Olaparib
RL: PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. having improved bioavailability of therapeutics)
IT 170729-80-3, Aprepitant
RL: PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. having improved bioavailability of therapeutics)
RN 170729-80-3 CAPLUS
CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
AU 2022248850 A1	AU 2022-248850	Register
CA 3212583 A1	CA 2022-3212583	Register
EP 4312978 A2	EP 2022-718916	Register|Federated Reg.
IN 202347072261 A	IN 2023-47072261	Register
JP 2024511208 T	JP 2023-559684	Register|Global Dossier
KR 2024021751 A	KR 2023-7037012	Register|Global Dossier
US 20220305125 A1	US 2022-17656702	Register|Global Dossier
US 20240075147 A1	US 2023-18487486	Register|Global Dossier
WO 2022207580 A2	WO 2022-EP58180	Register|Global Dossier
WO 2022207580 A3	WO 2022-EP58180	Register|Global Dossier
WO 2023174948 A2	WO 2023-EP56506	Register|Global Dossier
WO 2023174948 A3	WO 2023-EP56506	Register|Global Dossier

L5 ANSWER 5 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2022:2221248 CAPLUS Full-text
DOCUMENT NUMBER: 181:431761
TITLE: Small scale in vitro method to determine a potential bioequivalent equilibrium solubility range for fed human intestinal fluid
AUTHOR(S): Ines Silva, Maria; Khadra, Ibrahim; Pyper, Kate; Halbert, Gavin W.
CORPORATE SOURCE: Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, 161 Cathedral Street, Glasgow, G4 0RE, UK
SOURCE: European Journal of Pharmaceutics and Biopharmaceutics (2022), 177, 126-134
CODEN: EJPBEL; ISSN: 0939-6411
DIGITAL OBJECT ID: 10.1016/j.ejpb.2022.06.005
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
AB Intestinal drug soly. is a key parameter controlling oral absorption but varies both intra and inter individuals and between the fasted and fed states, with food intake known to alter the bioavailability of many compds. Intestinal soly. can be measured in vitro either using sampled fed human intestinal fluid (FeHIF) or simulated fed intestinal fluid (SIF) but neither approach is optimal. FeHIF is difficult to obtain and variable, while for fed SIF multiple recipes are available with no consensus on the ideal version. A recent study characterised FeHIF aspirates using a multidimensional approach and calcd. nine simulated media recipes that covered over ninety percent of FeHIF compositional variability. In this study the equil. soly. of thirteen drugs have been measured using the nine simulated media recipes and compared to multiple previous design of expt. (DoE) studies, which have examd. the impact of fed SIF media components on soly. The measured nine media soly. data set

is only statistically equiv. to the large scale 92 media DoE in 4 out of 13 drug comparisons, but has improved equivalence against small scale DoEs (9 or 10 media) with 6 out of 9 or 10 out of 12 (9 and 10 media resp.) equiv. Selective removal of non-biorelevant compns. from the 92 media DoE improves statistical equivalence to 9 out of 13 comparisons. The results indicate that soly. equivalence is linked to media component concns. and compns., the nine media system is measuring a similar soly. space to previous systems, with a narrower soly. range than the 92 point DoE but equiv. to smaller DoE systems. Phenytoin and tadalafil display a narrow soly. range, a behavior consistent with previous studies in fed and fasted states and only revealed through the multiple media approach. Custom DoE anal. of the nine media results to det. the most statistically significant component influencing soly. does not detect significant components. Indicating that the approach has a low statistical resoln. and is not appropriate if detn. of media component significance is required. This study demonstrates that it is possible to assess the fed intestinal equil. soly. envelope using the nine media recipes obtained from a multi-dimensional anal. of fed HIF. The derivation of the nine media compns. coupled with the results in this study indicate that the soly. results are more likely to reflect the fed intestinal soly. envelope than previous DoE studies and highlight that the system is worthy of further investigation.

CC 63-6 (Pharmaceuticals)

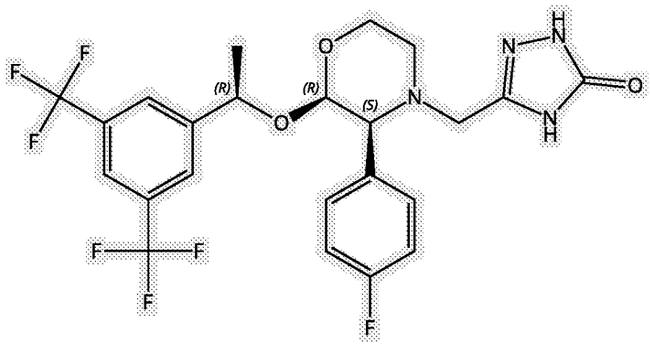
IT Lecithins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(small scale in vitro method to det. potential bioequivalent equil. soly. range for fed human intestinal fluid)

IT 53-86-1 57-41-0 57-88-5, Cholest-5-en-3-ol (3β)-, biological studies 110-16-7, 2-Butenedioic acid (2Z)-, biological studies 111-03-5 112-80-1, 9-Octadecenoic acid (9Z)-, biological studies 145-42-6 14265-44-2, Phosphate, biological studies 15687-27-1 23288-49-5 25614-03-3 49562-28-9 72509-76-3 72956-09-3 84625-61-6 107753-78-6 137862-53-4 170729-80-3 171596-29-5
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(small scale in vitro method to det. potential bioequivalent equil. soly. range for fed human intestinal fluid)

IT 170729-80-3
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(small scale in vitro method to det. potential bioequivalent equil. soly. range for fed human intestinal fluid)

RN 170729-80-3 CAPLUS

CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

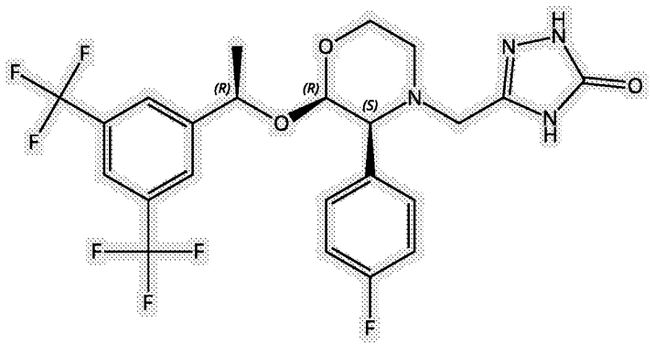
L5 ANSWER 6 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2022:1355958 CAPLUS Full-text
DOCUMENT NUMBER: 179:75293
TITLE: Stable antiemetic emulsions
INVENTOR(S): Bhagwatwar, Harshal Prabhakar; Nerurkar, Manoj
PATENT ASSIGNEE(S): Steps BioSciences, Inc., USA
ULTIMATE OWNER: STEPS BIOSCIENCES
ULTIMATE OWNER STANDARD: STEPS BIOSCIENCES
SOURCE: U.S. Pat. Appl. Publ., 11pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20220160722	A1	20220526	US 2021-17531216	20211119
PRIORITY APPLN. INFO.:			IN 2020-41050531 A	20201120

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
US 20220160722	A1	Alive	20220609

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASFORMULTNS 2022:1355958
AB Emulsion formulations and systems for the i.v. or parenteral administration. of neurokinin-1 (NK-1) receptor antagonists for treatment of emesis are provided. Methods for prepg. the stable NK-1 receptor antagonist emulsions and pharmaceutical formulations are further provided. The emulsion formulations are prepd. and characterized as a formulation and process that will allow an NK-1 receptor antagonist compd. to be incorporated into an emulsion for i.v. injection and remain stable during the shelf life of the formulation. Specifically, emulsion formulations have an oil phase that includes oil, ethanol, egg lecithin , and the further addn. of sodium oleate that is mixed with an aq. phase and processed to form the emulsion formulation.
IPCI A61K0031-5377 [I]; A61K0009-00 [I]; A61K0009-107 [I]; A61K0047-24 [I]; A61K0047-12 [I]; A61K0047-10 [I]; A61K0047-44 [I]
IPCR A61K0031-5377 [I]; A61K0009-00 [I]; A61K0009-107 [I]; A61K0047-10 [I]; A61K0047-12 [I]; A61K0047-24 [I]; A61K0047-44 [I]
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1
IT Castor oil
Coconut oil
Corn oil
Cottonseed oil
Egg yolk lecithins
Lecithins
Olive oil
Safflower oil
Sesame oil
Soybean oil
Triglycerides
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(stable antiemetic emulsions)
IT 57-50-1, Sucrose, biological studies 64-17-5, Ethanol, biological studies 111-62-6, Ethyl oleate 143-19-1, Sodium oleate 303-43-5, Cholesteryl oleate 544-35-4, Ethyl linoleate 604-33-1, Cholesteryl linoleate 37220-82-9, Glyceryl oleate 37348-65-5, Glyceryl linoleate 136745-48-7, Octyl glycerate 152167-64-1, Decyl glycerate 170729-80-3, Aprepitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(stable antiemetic emulsions)
IT 170729-80-3, Aprepitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(stable antiemetic emulsions)
RN 170729-80-3 CAPLUS
CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
US 20220160722 A1	US 2021-17531216	Register|Global Dossier

L5 ANSWER 7 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2022:139737 CAPLUS Full-text
DOCUMENT NUMBER: 177:284905
TITLE: Pharmaceutical emulsion comprising an aprepitant, pharmaceutical injections, and methods of preparing emulsions
INVENTOR(S): Amano, Yohei; Katagiri, Kazumi
PATENT ASSIGNEE(S): Kewpie Corporation, Japan; FBC (Shanghai) Pharmaceutical Technology Co., Ltd.
ULTIMATE OWNER: FBC SHANGHAI PHARMACEUTICAL TECHNOLOGY; FBC SHANGHAI PHARMACEUTICAL TECH CO LTD ; KEWPIE CORPORATION; FUBICHENG SHANGHAI MEDICAL TECH; FBC SHANGHAI PHARMACEUTICAL TECH
ULTIMATE OWNER STANDARD: FBC SHANGHAI PHARMACEUTICAL TECHNOLOGY; FBC SHANGHAI PHARMACEUTICAL TECH CO LTD ; Kewpie Corp; FUBICHENG SHANGHAI MEDICAL TECH; FBC SHANGHAI PHARMACEUTICAL TECH
SOURCE: PCT Int. Appl., 28pp.; Chemical Indexing Equivalent to 174:540291 (JP)
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2022014113	A1	20220120	WO 2021-JP15552	20210415
JP 6832468	B1	20210224	JP 2020-121438	20200715
JP 2022018370	A	20220127		
CA 3187858	A1	20220120	CA 2021-3187858	20210415
KR 2023040956	A	20230323	KR 2022-7045138	20210415
EP 4169515	A1	20230426	EP 2021-843280	20210415
US 20230310443	A1	20231005	US 2023-18015492	20230110

PRIORITY APPLN. INFO.: JP 2020-121438 A 20200715
WO 2021-JP15552 W 20210415

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
WO 2022014113	A1	Alive	20220203
JP 6832468	B1	Alive	20210304
JP 2022018370	A	Alive	20220224
CA 3187858	A1	Alive	20230216
KR 2023040956	A	Alive	20230420
EP 4169515	A1	Alive	20230427
US 20230310443	A1	Alive	20231012

AB The present invention pertains to an emulsion which contains an aprepitant, an emulsifier, an oil, a polyethylene glycol having an av. mol. wt. of 260-1100, and water, and to which ethanol is substantially not added. The content of the aprepitant is 0.50-0.90 w/v% based on the total amt., and the content of the emulsifier is 12.0-18 w/v%. The content of oil is 7.0-12.0 w/v %, and the content of polyethylene glycol is 0.5-10.0 w/v %. The av. particle diam. of the emulsion is 60-140 nm. According to the present invention, provided is an aprepitant-contg. emulsion having excellent stability without substantially adding ethanol.

IPCI A61K0031-5377 [I]; A61K0009-107 [I]; A61K0047-10 [I]; A61K0047-24 [I]; A61K0047-44 [I]; A61P0001-08 [I]

IPCR A61K0031-5377 [I]; A61K0009-107 [I]; A61K0047-10 [I]; A61K0047-24 [I]; A61K0047-44 [I]; A61P0001-08 [I]

CC 63-6 (Pharmaceuticals)

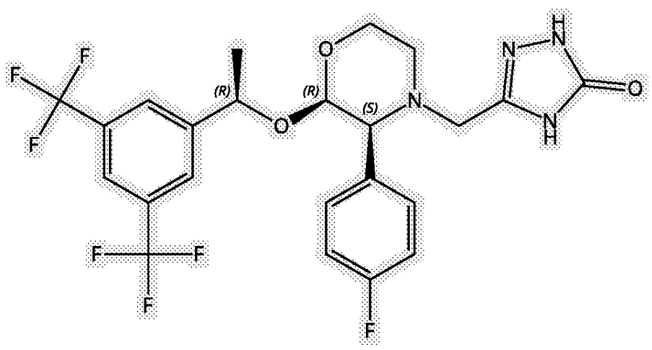
IT Egg yolk lecithins
Phospholipids
Polyoxyalkylenes
Soybean oil
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical emulsion comprising aprepitant, pharmaceutical injections, and methods of prepg. emulsions)

IT 170729-80-3
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical emulsion comprising aprepitant, pharmaceutical injections, and methods of prepg. emulsions)

IT 170729-80-3
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical emulsion comprising aprepitant, pharmaceutical injections, and methods of prepg. emulsions)

RN 170729-80-3 CAPLUS

CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
CA 3187858 A1	CA 2021-3187858	Register
EP 4169515 A1	EP 2021-843280	Register|Federated Reg.
JP 2022018370 A	JP 2020-121438	Register|Global Dossier
JP 6832468 B1	JP 2020-121438	Register|Global Dossier
KR 2023040956 A	KR 2022-7045138	Register|Global Dossier
US 20230310443 A1	US 2023-18015492	Register|Global Dossier
WO 2022014113 A1	WO 2021-JP15552	Register|Global Dossier

L5 ANSWER 8 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2021:2591917 CAPLUS Full-text
DOCUMENT NUMBER: 177:123225

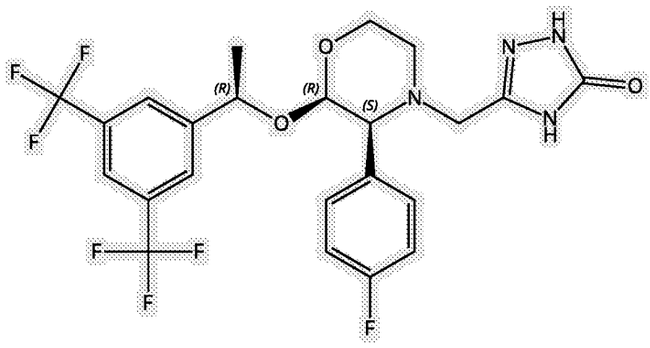
TITLE: Preparation method of aprepitant emulsion injection for preventing nausea and emesis
INVENTOR(S): Guo, Shuer; Qin, Zhijun
PATENT ASSIGNEE(S): Guangzhou Manxiang Pharmaceutical Co., Ltd., Peop. Rep. China
ULTIMATE OWNER: GUANGZHOU MAXENMED MEDICINE
ULTIMATE OWNER STANDARD: GUANGZHOU MAXENMED MEDICINE
SOURCE: Faming Zhuanli Shenqing, 9pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 113712915	A	20211130	CN 2021-10018100	20210107

PRIORITY APPLN. INFO.: CN 2021-10018100 20210107
PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
CN 113712915	A	Transitional	20240502

OTHER SOURCE(S): CASFORMULTNS 2021:2591917
AB The invention aprepitant emulsion injection is prepd. from (by wt%) aprepitant 0.2-1.2, pH regulator 0.25-0.75, permeation pressure regulator 3-8, injection water 56-75, emulsifier 12-15, cosolvent 2-5, and injection oil 5-15. The emulsifier is hydrogenated soybean lecithin or hydrogenated soybean phosphatidylcholine. The pH regulator is sodium hydroxide, sodium citrate, sodium dihydrogen phosphate or sodium oleate. The permeation pressure regulator is xylitol, sorbitol, mannitol or sucrose. The cosolvent is ethanol, glycerol, propylene glycol and polyethylene glycol. The injection oil is soybean oil, peanut oil, hydrogenated corn oil, triglyceride, medium-chain triglyceride, sesame oil and/or sunflower seed oil. By controlling content of emulsifier and shearing rotation speed, homogenization pressure and homogenization temp. in emulsion prepn. process, the invention preps. aprepitant emulsion injection with good oxidn. resistance and emulsification effect, and has operability, simple process and low device loss.
IPCI A61K0009-107; A61K0047-24; A61K0031-5377; A61P0001-08; A61P0035-00
IPCR A61K0009-107 [I]; A61K0031-5377 [I]; A61K0047-24 [I]; A61P0001-08 [I]; A61P0035-00 [I]
CC 63-6 (Pharmaceuticals)
IT Corn oil
Soya lecithins
RL: MOA (Modifier or additive use); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hydrogenated; prepn. method of aprepitant emulsion injection for preventing nausea and emesis)
IT 170729-80-3, Aprepitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. method of aprepitant emulsion injection for preventing nausea and emesis)
IT 170729-80-3, Aprepitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. method of aprepitant emulsion injection for preventing nausea and emesis)
RN 170729-80-3 CAPLUS
CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
CN 113712915 A	CN 2021-10018100	Register|Global Dossier

L5 ANSWER 9 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2021:1541826 CAPLUS Full-text
DOCUMENT NUMBER: 175:329880
TITLE: Aprepitant ready-to-use injection emulsion compositions
INVENTOR(S): Akasapu, Prem Sagar; Subramanian, Veerappan; Subramanian, Ilango
PATENT ASSIGNEE(S): Somerset Therapeutics LLC, USA
ULTIMATE OWNER: SOMERSET THERAPEUTICS LLC
ULTIMATE OWNER STANDARD: SOMERSET THERAPEUTICS LLC
SOURCE: U.S. Pat. Appl. Publ., 8pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

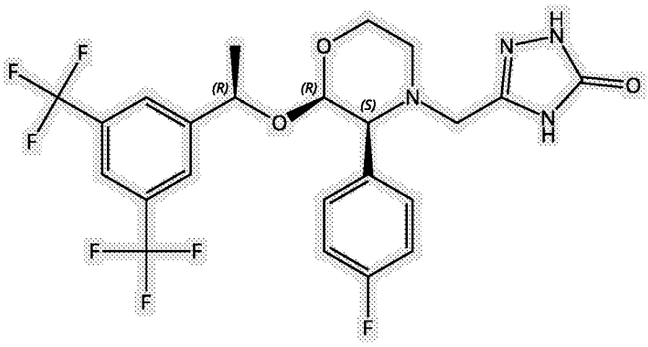
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20210212933	A1	20210715	US 2021-17147556	20210113
US 11517522	B2	20221206		

PRIORITY APPLN. INFO.: US 2020-62961039 P 20200114
PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
US 20210212933	A1	Alive	20210722
US 11517522	B2	Alive	20221215

OTHER SOURCE(S): CASFORMULTNS 2021:1541826
AB The present invention provides an emulsion compn. comprising aprepitant for treatment of emesis. Particularly, the invention is a ready-to-use emulsion compns. comprising aprepitant and medium chain triglycerides for administration by i.v. infusion, wherein the emulsion compn. is also free of ethanol. Further, the invention also provides processes of prepg. such compns. and their use for the prevention and control of acute and delayed chemotherapy-induced nausea and vomiting, and/or for prevention of postoperative nausea and vomiting.
IPCI A61K0009-00 [I]; A61K0009-107 [I]; A61K0047-14 [I]; A61M0005-24 [I]; A61K0031-5377 [I]; A61K0009-00 [I]; A61K0047-14 [I]; A61K0009-107 [I]; A61K0031-5377 [I]; A61M0005-24 [I]
IPCR A61K0009-00 [I]; A61K0009-107 [I]; A61K0031-5377 [I]; A61K0047-14 [I]; A61M0005-24 [I]
CC 63-6 (Pharmaceuticals)
IT Lecithins
Medium-chain glycerides
Polyoxyalkylenes
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(aprepitant ready-to-use injection emulsion compns.)
IT 170729-80-3, Aprepitant
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aprepitant ready-to-use injection emulsion compns.)
IT 170729-80-3, Aprepitant
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aprepitant ready-to-use injection emulsion compns.)
RN 170729-80-3 CAPLUS
CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
US 11517522 B2	US 2021-17147556	Register|Global Dossier
US 20210212933 A1	US 2021-17147556	Register|Global Dossier

L5 ANSWER 10 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2021:685825 CAPLUS Full-text
DOCUMENT NUMBER: 178:140851
TITLE: Aprepitant submicroemulsion injection capable of being autoclaved, and its preparation method
INVENTOR(S): Qin, Linghao; Li, Yusheng; Zhu, Wanye; Wang, Wanting
PATENT ASSIGNEE(S): Guangdong Pharmaceutical University, Peop. Rep. China
SOURCE: Faming Zhuanli Shenqing, 19pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 112535661	A	20210323	CN 2020-11524237	20201222
CN 112535661	B	20230407		

PRIORITY APPLN. INFO.: CN 2020-11524237 20201222
PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
CN 112535661	A	Alive	20210408
CN 112535661	B	Alive	20230427

OTHER SOURCE(S): CASFORMULTNS 2021:685825
AB A safe aprepitant submicroemulsion injection capable of being autoclaved having high efficiency, good stability and sterilization effect, and wide application in medicine field is provided. The aprepitant submicroemulsion injection comprises: polyethylene glycol 15hydroxystearate, phospholipids, aprepitant, oil for injection, emulsifier, co-emulsifier, solubilizer, stabilizer, isotonic agent, pH

regulator and water for injection. The prepn. method comprises the following steps: (1) mixing aprepitant, injection oil and solubilizer, dissolving and dispersing with alc., and removing the alc. to obtain an oil phase mixt.; (2) stirring and mixing the emulsifier, co-emulsifier, stabilizer, isotonic agent and water for injection, and heat to dissolve to obtain the water phase mixt.; and (3) adding the oil phase mixt. to the water phase mixt., prepg. the emulsion, and autoclaving to obtain the aprepitant submicroemulsion injection. The aprepitant submicroemulsion injection is used in the prepn. of a medicine for treating nausea and vomiting.

IPCI A61K0009-107; A61K0031-5377; A61K0047-24; A61K0047-14; A61K0047-18; A61P0001-08; A61L0002-07

IPCR A61K0009-107 [I]; A61K0031-5377 [I]; A61K0047-14 [I]; A61K0047-18 [I]; A61K0047-24 [I]; A61L0002-07 [I]; A61P0001-08 [I]

CC 63-6 (Pharmaceuticals)

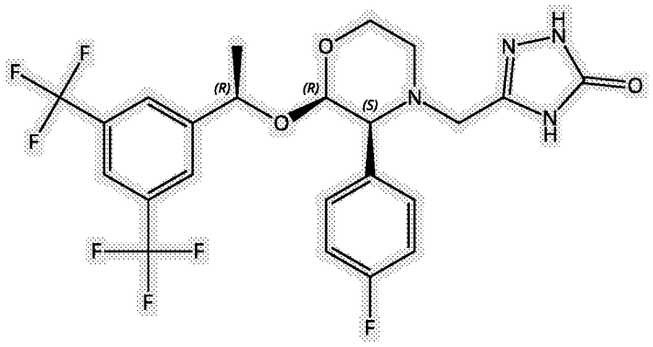
IT Amino acids
Egg yolk lecithins
Oils
Phospholipids
RL: MOA (Modifier or additive use); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aprepitant submicroemulsion injection capable of being autoclaved, and its prepn. method)

IT 56-41-7, L-Alanine, biological studies 56-84-8, L-Aspartic acid, biological studies 56-86-0, L-Glutamic acid, biological studies 63-91-2, L-Phenylalanine, biological studies 73-32-5, L-Isoleucine, biological studies 170729-80-3, Aprepitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aprepitant submicroemulsion injection capable of being autoclaved, and its prepn. method)

IT 170729-80-3, Aprepitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aprepitant submicroemulsion injection capable of being autoclaved, and its prepn. method)

RN 170729-80-3 CAPLUS

CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
CN 112535661 A	CN 2020-11524237	Register|Global Dossier
CN 112535661 B	CN 2020-11524237	Register|Global Dossier

L5 ANSWER 11 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2021:481715 CAPLUS Full-text
DOCUMENT NUMBER: 174:540291
TITLE: Pharmaceutical emulsion comprising an aprepitant, pharmaceutical injections, and methods of preparing

emulsions
INVENTOR(S): Amano, Yohei; Katagiri, Kazumi
PATENT ASSIGNEE(S): Kewpie Corporation, Japan; FBC (Shanghai) Pharmaceutical Technology Co., Ltd.
ULTIMATE OWNER: FUBICHENG SHANGHAI MEDICAL TECH; FBC SHANGHAI PHARMACEUTICAL TECH; FBC SHANGHAI PHARMACEUTICAL TECHNOLOGY; FBC SHANGHAI PHARMACEUTICAL TECH CO LTD ; KEWPIE CORPORATION
ULTIMATE OWNER STANDARD: FUBICHENG SHANGHAI MEDICAL TECH; FBC SHANGHAI PHARMACEUTICAL TECH; FBC SHANGHAI PHARMACEUTICAL TECHNOLOGY; FBC SHANGHAI PHARMACEUTICAL TECH CO LTD ; Kewpie Corp
SOURCE: Jpn. Tokkyo Koho, 15pp.; Chemical Indexing Equivalent to 177:284905 (WO)
CODEN: JTXXFF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 6832468	B1	20210224	JP 2020-121438	20200715
JP 2022018370	A	20220127		
CA 3187858	A1	20220120	CA 2021-3187858	20210415
WO 2022014113	A1	20220120	WO 2021-JP15552	20210415
KR 2023040956	A	20230323	KR 2022-7045138	20210415
EP 4169515	A1	20230426	EP 2021-843280	20210415
CN 113952299	A	20220121	CN 2021-10772526	20210708
CN 117017915	A	20231110	CN 2023-11089804	20210708
US 20230310443	A1	20231005	US 2023-18015492	20230110

PRIORITY APPLN. INFO.:

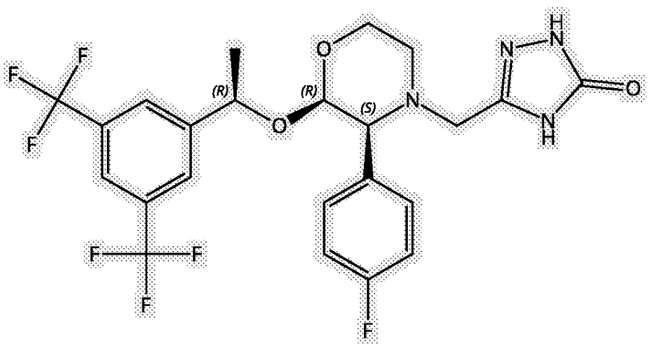
JP 2020-121438	A	20200715
WO 2021-JP15552	W	20210415
CN 2021-10772526	A3	20210708

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
JP 6832468	B1	Alive	20210304
JP 2022018370	A	Alive	20220224
CA 3187858	A1	Alive	20230216
WO 2022014113	A1	Alive	20220203
KR 2023040956	A	Alive	20230420
EP 4169515	A1	Alive	20230427
CN 113952299	A	Alive	20220203
CN 117017915	A	Alive	20231116
US 20230310443	A1	Alive	20231012

OTHER SOURCE(S): CASFORMULTNS 2021:481715
AB The emulsion comprises: an aprepitant, an emulsifier, an oil, polyethylene glycol and water, with substantially no addn. of ethanol. The emulsion comprises a pH regulator and having a pH of 8.0-9.0. The content of the aprepitant is 0.50 w/v% or more and 0.90 w/v% or less based on the total amt., and the content of the emulsifier is 12.0 w/v% or more and 12.0 w/v% or more based on the total amt. The emulsion is 0 w/v% or less, the emulsion in which the emulsifier is a phospholipid. According to the present invention, provided is an aprepitant-contg. emulsion having excellent stability without substantially adding ethanol.
IPCI A61K0031-5377 [I]; A61K0009-107 [I]; A61P0001-08 [I]; A61K0047-10 [I]; A61K0047-24 [I]; A61K0047-44 [I]; A61K0009-107 [I]; A61K0047-10 [I]; A61K0031-5377 [I]; A61P0001-08 [I]; A61K0047-24 [I]; A61K0047-44 [I]
IPCR A61K0031-5377 [I]; A61K0009-107 [I]; A61K0047-10 [I]; A61K0047-24 [I]; A61K0047-44 [I]; A61P0001-08 [I]
CC 63-6 (Pharmaceuticals)
IT Egg yolk lecithins
Phospholipids
Polyoxyalkylenes
Soybean oil
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical emulsion comprising aprepitant, pharmaceutical injections, and methods of prepg. emulsions)
IT 170729-80-3
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical emulsion comprising aprepitant, pharmaceutical

injections, and methods of prepg. emulsions)
IT 170729-80-3
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical emulsion comprising aprepitant, pharmaceutical injections, and methods of prepg. emulsions)
RN 170729-80-3 CAPLUS
CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
CA 3187858 A1	CA 2021-3187858	Register
CN 113952299 A	CN 2021-10772526	Register|Global Dossier
CN 117017915 A	CN 2023-11089804	Register|Global Dossier
EP 4169515 A1	EP 2021-843280	Register|Federated Reg.
JP 2022018370 A	JP 2020-121438	Register|Global Dossier
JP 6832468 B1	JP 2020-121438	Register|Global Dossier
KR 2023040956 A	KR 2022-7045138	Register|Global Dossier
US 20230310443 A1	US 2023-18015492	Register|Global Dossier
WO 2022014113 A1	WO 2021-JP15552	Register|Global Dossier

L5 ANSWER 12 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2020:2334591 CAPLUS Full-text
DOCUMENT NUMBER: 174:387650
TITLE: Enhanced transdermal permeation of BCS class IV aprepitant using binary ethosome: Optimization, characterization and ex vivo permeation
AUTHOR(S): Abouhussein, Dalia M. N.
CORPORATE SOURCE: Department of Pharmaceutics, Egyptian Drug Authority Formerly Known As National Organization for Drug Control and Research (NODCAR), Egypt
SOURCE: Journal of Drug Delivery Science and Technology (2021), 61, 102185
CODEN: JDDSAL; ISSN: 1773-2247
DIGITAL OBJECT ID: 10.1016/j.jddst.2020.102185
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
AB Aprepitant (APR) belongs to the Biopharmaceutics Classification System (BCS) class IV that is characterized by both low soly. and permeability. This study aims to develop a new transdermal APR nanovesicle for chemotherapy-induced nausea and vomiting. APR binary ethosomes (BEs) were developed using 32 factorial design where two independent variables namely; wt. of lecithin and propylene glycol were studied. The formulations were fully characterized through entrapment efficiency (EE),

vesicle size (VS) and zeta potential (ZP). The optimized formulation was designated through the desirability value obtained by Design Expert program, visualized using transmission electron microscope (TEM) and studied for stability. Then the optimized formulation was incorporated in 0.8% carbopol 934 gel which was characterized and tested for in vitro and ex vivo release. F9 contg. 100 mg lecithin and 2.5 g propylene glycol was selected to be the optimum formulation. It showed desirability value of 0.958 as it displayed 89.6% EE, VS of 77 nm, -51.1 as ZP in addn. to adequate stability. The APR BE gel showed satisfactory phys., mech., rheol. and occlusive properties. The optimum formulation showed 4.9 folds higher permeation than APR suspension. BE gel exhibited a promising dosage form for the transdermal delivery of APR.

CC 63-5 (Pharmaceuticals)

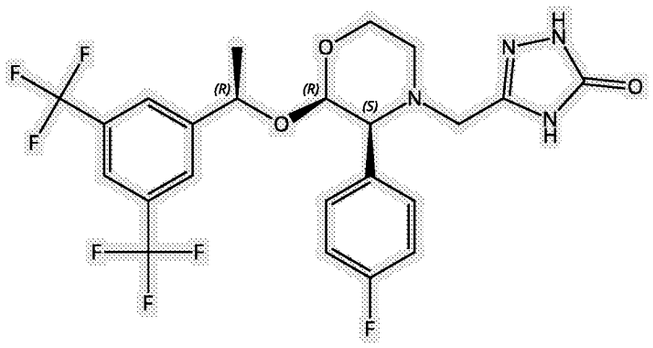
IT Lecithins
Phospholipids
RL: MOA (Modifier or additive use); USES (Uses)
(optimum formulation of aprepitant binary ethosomes gel showed satisfactory phys., mech., rheol. and occlusive properties for transdermal delivery)

IT 170729-80-3
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(optimum formulation of aprepitant binary ethosomes gel showed satisfactory phys., mech., rheol. and occlusive properties for transdermal delivery)

IT 170729-80-3
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(optimum formulation of aprepitant binary ethosomes gel showed satisfactory phys., mech., rheol. and occlusive properties for transdermal delivery)

RN 170729-80-3 CAPLUS

CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

OS.CITING REF COUNT: 10 THERE ARE 10 CAPLUS RECORDS THAT CITE THIS RECORD (10 CITINGS)

REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 13 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN

ACCESSION NUMBER: 2020:485442 CAPLUS Full-text

DOCUMENT NUMBER: 177:51750

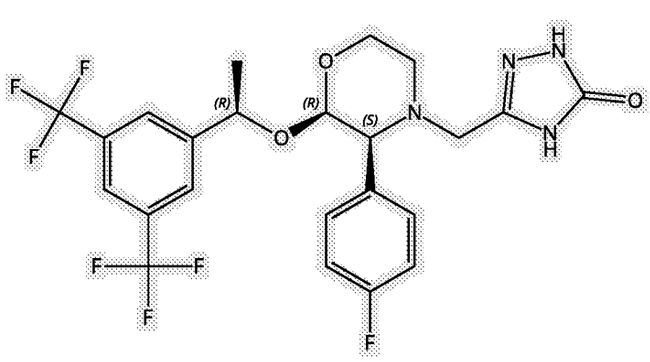
TITLE: Aprepitant Intravenous Emulsion Based on Ion Pairing/Phospholipid Complex for Improving Physical and Chemical Stability During Thermal Sterilization

AUTHOR(S): Zhang, Xinyu; Wei, Ying; Cao, Zhijun; Xu, Ying; Lu, Cong; Zhao, Meiqi; Gou, Jingxin; Yin, Tian; Zhang, Yu; He, Haibing; Wang, Yanjiao; Tang, Xing

CORPORATE SOURCE: Department of Pharmaceutics, Shenyang Pharmaceutical University, Shenyang, Peop. Rep. China

SOURCE: AAPS PharmSciTech (2020), 21(3), 75

CODEN: AAPHFZ; ISSN: 1530-9932
DIGITAL OBJECT ID: 10.1208/s12249-019-1605-7
PUBLISHER: Springer
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
AB An aprepitant (APT) cholesteryl hemisuccinate (CHEMS) ion pair complex emulsion (AIPE) with high lecithin content was prepd. to improve sterilization stability through the film dispersion homogenization method; therefore, it could be a promising delivery system of APT. Medium-chain triglycerides (MCT) was selected as the oil phase to improve the soly. and stability of APT in oil phase. DSC, XRD, FT-IR, and 1H-NMR spectroscopies confirmed that the APT-CHEMS ion pair (AIP) was formed between CHEMS and APT. The formation of AIP significantly increased the hydrophobicity of APT, allowing it to be completely embedded in the oil phase core to improve chem. stability and decrease hydrolysis of APT in the water phase. Also, CHEMS had a strong affinity with lecithin and could stabilize lipid membranes, forming a stronger and thicker interface membrane to increase the phys. stability of AIPE. As a result, AIPE could withstand autoclaving at 120°C for 8 min without any change of particle size or content. Furthermore, AIPE with a potential of - 53.4 mV remained stable through spatial repulsion during sterilization. The encapsulation efficiency of AIPE was over 90% and the particle size was 106.8 ± 65.62 nm(0.286). Pharmacokinetic study in rats was comparable with that of CINVANTI which yielded a relative bioavailability of 114.31% indicating that the AIPE had similar pharmacokinetic processes in vivo with the analog of CINVANTI. The AUC0-t of the AIPE was 4.31-fold that of the APT soln.
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1
IT Egg yolk lecithins
Medium-chain glycerides
Soya lecithins
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aprepitant i.v. emulsion based on ion pairing/phospholipid complex for improving phys. and chem. stability during thermal sterilization)
IT 170729-80-3
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aprepitant i.v. emulsion based on ion pairing/phospholipid complex for improving phys. and chem. stability during thermal sterilization)
IT 170729-80-3
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aprepitant i.v. emulsion based on ion pairing/phospholipid complex for improving phys. and chem. stability during thermal sterilization)
RN 170729-80-3 CAPLUS
CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

OS.CITING REF COUNT: 6 THERE ARE 6 CAPLUS RECORDS THAT CITE THIS RECORD (6 CITINGS)
REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

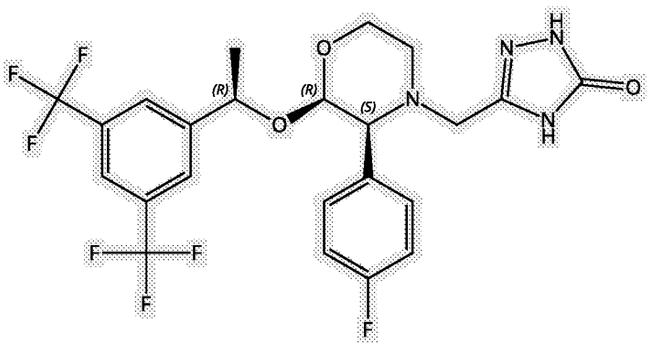
L5 ANSWER 14 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2020:456048 CAPLUS Full-text
DOCUMENT NUMBER: 177:51649
TITLE: Small scale design of experiment investigation of equilibrium solubility in simulated fasted and fed intestinal fluid
AUTHOR(S): McPherson, Stephanie; Perrier, Jeremy; Dunn, Claire; Khadra, Ibrahim; Davidson, Scott; Ainousah, Bayan; Wilson, Clive G.; Halbert, Gavin
CORPORATE SOURCE: Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow, G4 0RE, UK
SOURCE: European Journal of Pharmaceutics and Biopharmaceutics (2020), 150, 14-23
CODEN: EJPBEL; ISSN: 0939-6411
DIGITAL OBJECT ID: 10.1016/j.ejpb.2020.01.016
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
AB It is widely recognized that drug soly. within the gastrointestinal tract (GIT) differs from values detd. in a simple aq. buffer and to circumvent this problem measurement in biorelevant fluids is detd. Biorelevant fluids are complex mixts. of components (sodium taurocholate, lecithin, sodium phosphate, sodium chloride, pancreatin and sodium oleate) at various concns. and pH levels to provide systems simulating fasted (FaSSIF) or fed (FeSSIF) intestinal media. Design of Expt. (DoE) studies have been applied to investigate FaSSIF and FeSSIF and indicate that a drugs equil. soly. varies over orders of magnitude, is influenced by the drug type and individual or combinations of media components, with some of these interactions being drug specific. Although providing great detail on the drug media interactions these studies are resource intensive requiring up to ninety individual expts. for FeSSIF. In this paper a low sample no. or reduced DoE system has been investigated by restricting components with minimal soly. impact to a single value and only investigating variations in the concns. of sodium taurocholate, lecithin, sodium oleate, pH and addnl. in the case of fed media, monoglyceride. This reduces the expts. required to ten (FaSSIF) and nine (FeSSIF). Twelve poorly sol. drugs (Ibuprofen, Valsartan, Zafirlukast, Indomethacin, Fenofibrate, Felodipine, Probucol, Tadalafil, Carvedilol, Aprepitant, Bromocriptine and Itraconazole) were investigated and the results compared to published DoE studies and literature soly. values in human intestinal fluid (HIF), FaSSIF or FeSSIF. The soly. range detd. by the reduced DoE is statistically equiv. to the larger scale published DoE results in over eighty five percent of the cases. The reduced DoE range also covers HIF, FaSSIF or FeSSIF literature soly. values. In addn. the reduced DoE provides lowest measured soly. values that agree with the published DoE values in ninety percent of the cases. However, the reduced DoE only identified single and in some cases none of the major components influencing soly. in contrast to the larger published DoE studies which identified multiple individual components and component interactions. The identification of significant components within the reduced DoE was also dependent upon the drug and system under investigation. The study demonstrates that the lower exptl. no. reduces statistical power of the DoE to resolve the impact of media components on soly. However, in a situation where only the soly. range is required the reduced DoE can provide the desired information, which will be of benefit during in vitro development studies. Further refinements are possible to extend the reduced DoE protocol to improve biorelevance and application into areas such as PBPK modeling.
CC 63-5 (Pharmaceuticals)
IT Lecithins
Monoglycerides
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(small scale design of expt. investigation of equil. soly. in simulated fasted and fed intestinal fluid)
IT 53-86-1 143-19-1 145-42-6 15687-27-1 23288-49-5 25614-03-3

49562-28-9 72509-76-3 72956-09-3 84625-61-6 107753-78-6
137862-53-4 170729-80-3 171596-29-5
RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(small scale design of expt. investigation of equil. soly. in simulated fasted and fed intestinal fluid)

IT 170729-80-3
RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(small scale design of expt. investigation of equil. soly. in simulated fasted and fed intestinal fluid)

RN 170729-80-3 CAPLUS

CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

OS.CITING REF COUNT: 17 THERE ARE 17 CAPLUS RECORDS THAT CITE THIS RECORD (17 CITINGS)
REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 15 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2020:418384 CAPLUS Full-text
DOCUMENT NUMBER: 172:285814
TITLE: Preparation of nanosuspension comprising nanocrystals of active pharmaceutical ingredients with little or no stabilizing agents
INVENTOR(S): Martin, Brice; Mignet, Nathalie; Corvis, Yohann
PATENT ASSIGNEE(S): Centre National de la Recherche Scientifique (CNRS), Fr.; Universite Paris Descartes; Institut National de la Sante et de la Recherche Medicale (INSERM); Ecole Nat Superieure de Chimie Paris
SOURCE: PCT Int. Appl., 66pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2020043735	A1	20200305	WO 2019-EP72873		20190827
EP 3616688	A1	20200304	EP 2018-306138		20180827
EP 3843705	A1	20210707	EP 2019-756406		20190827
EP 3843705	B1	20231129			
EP 3843705	C0	20231129			
US 20210315831	A1	20211014	US 2021-17269802		20210219
PRIORITY APPLN. INFO.:			EP 2018-306138	A	20180827
			WO 2019-EP72873	W	20190827

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE

WO 2020043735	A1	Dead	20230427
EP 3616688	A1	Dead	20210909
EP 3843705	A1	Indeterminate	20240418
EP 3843705	B1	Indeterminate	20240418
EP 3843705	C0	Alive	20240215
US 20210315831	A1	Alive	20211121

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB The invention relates to a method for manufg. a nanostructured powder comprising nanocryst. agglomerates contg. active pharmaceutical ingredient (API) in its cryst. form, said method comprising (i) Prepg. a first soln. comprising API and an API solvent; (ii) Mixing the first soln. with a second soln. comprising an API antisolvent and optionally a stabilizing agent P1 to obtain a third mixt.; (iii) Evapg. the third mixt. until both the API solvent and the API antisolvent are evapd., advantageously under vacuum; characterized in that when the stabilizing agent P1 is present, the third mixt. has a stabilizing agent P1 to API wt. ratio equal or less than 5, preferably less than 2. The invention also concerns a nanostructured powder and a nanosuspension.

IPCI A61K0009-14 [I]; A61K0009-51 [I]; A61K0031-365 [I]; A61K0031-7048 [I]; A61P0035-00 [I]

IPCR A61K0009-14 [I]; A61K0009-51 [I]; A61K0031-365 [I]; A61K0031-7048 [I]; A61P0035-00 [I]

CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1

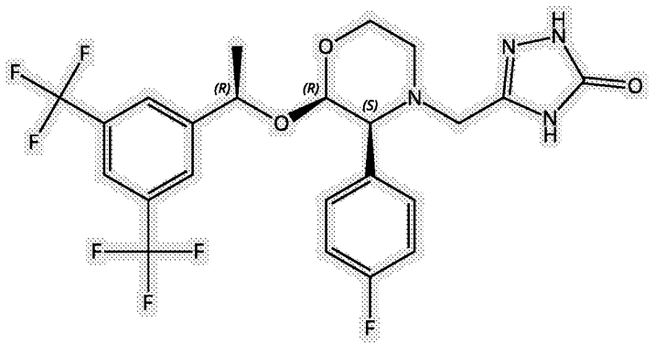
IT Albumins
Asialofetuins
Egg yolk lecithins
Lecithins
Soya phosphatidylcholines
Transferrins
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. of nanosuspension comprising nanocrystals of active pharmaceutical ingredients with little or no stabilizing agents)

IT 50-02-2, Dexamethasone 50-23-7, Hydrocortisone 50-24-8, Prednisolone 52-01-7, Spironolactone 53-86-1, Indometacin 61-68-7, Mefenamic acid 126-07-8, Griseofulvin 127-40-2, Lutein 137-66-6, Ascorbyl palmitate 153-18-4, Rutin 458-37-7, Curcumin 501-36-0, Resveratrol 520-33-2, Hesperetin 528-48-3, Fisetin 1198-77-2, Monosodium urate 1397-89-3, Amphotericin B 2030-63-9, Clofazimine 2608-24-4, Piposulfan 3681-99-0, Puerarin 7689-03-4, Camptothecin 10238-21-8, Glibenclamide 15307-86-5, Diclofenac acid 15687-27-1, Ibuprofen 17230-88-5, Danazol 19685-09-7, Hydroxycamptothecin 21967-41-9, Baicalin 22071-15-4, Ketoprofen 22204-53-1, Naproxen 22888-70-6, Silybin 22916-47-8, Miconazole 23214-92-8, Doxorubicin 28957-04-2, Oridonin 29990-52-1, Methyltryptophan 31431-39-7, Mebendazole 33069-62-4, Paclitaxel 49562-28-9, Fenofibrate 54965-21-8, Albendazole 59865-13-3, Cyclosporine 63675-72-9, Nisoldipine 66085-59-4, Nimodipine 71125-38-7, Meloxicam 73590-58-6, Omeprazole 73963-72-1, Cilostazole 79902-63-9, Simvastatin 80841-47-0, Asulacrine 83905-01-5, Azithromycin 84625-61-6, Itraconazole 88426-33-9, Buparvaquone 98093-93-7, Riccardin D 114977-28-5, Docetaxel 116122-36-2, Breviscapine 129722-12-9, Aripiprazole 141374-81-4, Tarazepide 145040-37-5, Candesartan cilexetil 146939-27-7, Ziprasidone 147362-57-0, Loviride 153559-49-0, Bexarotene 154598-52-4, Efavirenz 169590-42-5, Celecoxib 170729-80-3, Aprepitant 183133-96-2, Cabazitaxel 206361-99-1, Darunavir 330784-47-9, Avanafil 1257228-26-4, Amoitone B
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. of nanosuspension comprising nanocrystals of active pharmaceutical ingredients with little or no stabilizing agents)

IT 170729-80-3, Aprepitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. of nanosuspension comprising nanocrystals of active pharmaceutical ingredients with little or no stabilizing agents)

RN 170729-80-3 CAPLUS

CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
EP 3616688 A1	EP 2018-306138	Register|Federated Reg.
EP 3843705 A1	EP 2019-756406	Register|Federated Reg.
EP 3843705 B1	EP 2019-756406	Register|Federated Reg.
EP 3843705 C0	EP 2019-756406	Register|Federated Reg.
US 20210315831 A1	US 2021-17269802	Register|Global Dossier
WO 2020043735 A1	WO 2019-EP72873	Register|Global Dossier

L5 ANSWER 16 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2020:245679 CAPLUS Full-text
DOCUMENT NUMBER: 172:258881
TITLE: Emulsion containing high proportion emulsifier and preparation method thereof
INVENTOR(S): Niu, Yawei; Xu, Wendong; Tang, Shunzhi; Yuan, Cheng; Fu, Yuping; Guan, Weijian; Wang, Guocai; Mou, Xiaonan; Li, Jirong; Li, Yao
PATENT ASSIGNEE(S): Guangzhou Baiyunshan Hanfang Pharmaceutical Co., Ltd., Peop. Rep. China
ULTIMATE OWNER: GUANGZHOU BAIYUNSHAN PHARMACEUTICAL HOLDINGS CO., LTD.
ULTIMATE OWNER STANDARD: Guangzhou Baiyunshan Pharma
SOURCE: Faming Zhuanli Shenqing, 15pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

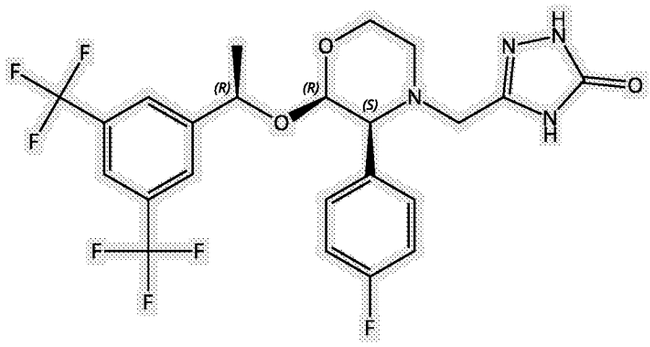
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 110772482	A	20200211	CN 2019-11215436	20191202

PRIORITY APPLN. INFO.: CN 2019-11215436 20191202
PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
CN 110772482	A	Dead	20230511

AB The invention discloses an emulsion contg. high proportion emulsifier and prepn. method thereof, which has the advantages of high drug loading and high bioavailability. The emulsion contg. high proportion emulsifier comprises the following raw materials in percentage by wt.: oil phase solvent 10-30%, emulsifier 10-30%, co-emulsifier 1-5%, volatile assistant 1-5%, stabilizer 0.05-0.6%, isoosmotic adjusting agent 1-5%, viscosity regulator 1-10%, active pharmaceutical ingredient 1-5%, and the balance of injection water.
IPCI A61K0009-107; A61K0047-26; A61K0047-44; A61K0047-14; A61K0047-10; A61K0031-5377
IPCR A61K0009-107 [I]; A61K0031-5377 [I]; A61K0047-10 [I]; A61K0047-14 [I]; A61K0047-26 [I]; A61K0047-44 [I]

CC 63-7 (Pharmaceuticals)
IT Carbohydrates
Castor oil
Egg yolk lecithins
Fish oil
Fructooligosaccharides
Olive oil
Phosphatidylcholines
Phosphatidylglycerols
Soya lecithins
Soybean oil
Triglycerides
RL: MOA (Modifier or additive use); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(emulsion contg. high proportion emulsifier and prepn. method thereof)
IT 170729-80-3, Aprepitant 552292-08-7, Rolapitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(emulsion contg. high proportion emulsifier and prepn. method thereof)
IT 170729-80-3, Aprepitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(emulsion contg. high proportion emulsifier and prepn. method thereof)
RN 170729-80-3 CAPLUS
CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
CN 110772482 A	CN 2019-11215436	Register|Global Dossier

L5 ANSWER 17 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2019:1744396 CAPLUS Full-text
DOCUMENT NUMBER: 171:388517
TITLE: Aqueous formulations for insoluble drugs
INVENTOR(S): Chen, Andrew Xian; Islam, Mohammad Saiful; Chu, Jan-Jon; Xu, Jianmin
PATENT ASSIGNEE(S): USA
SOURCE: PCT Int. Appl., 84pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2019173526	A1	20190912	WO 2019-US21029	20190306
CA 3088017	A1	20190912	CA 2019-3088017	20190306

AU 2019231699	A1	20200716	AU 2019-231699		20190306
AU 2019231699	B2	20230309			
CN 111867562	A	20201030	CN 2019-80017435		20190306
CN 111867562	B	20230707			
EP 3761961	A1	20210113	EP 2019-764228		20190306
JP 2021515048	T	20210617	JP 2020-570411		20190306
US 20200368159	A1	20201126	US 2020-16993017		20200813
US 11541006	B2	20230103			
PRIORITY APPLN. INFO.:			US 2018-62639710	P	20180307
			WO 2019-US21029	W	20190306

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
WO 2019173526	A1	Dead	20221110
CA 3088017	A1	Alive	20201121
AU 2019231699	A1	Alive	20201121
AU 2019231699	B2	Alive	20230316
CN 111867562	A	Alive	20201120
CN 111867562	B	Alive	20230720
EP 3761961	A1	Alive	20210118
JP 2021515048	T	Alive	20210624
US 20200368159	A1	Alive	20221020
US 11541006	B2	Alive	20230119

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OTHER SOURCE(S): CASFORMULTNS 2019:1744396

AB This invention relates to clear one-phase liq. formulation vehicles comprising lecithin , MCT, bile salt and water. In an aspect, this invention provides a clear and one-phase aq. liq. compn. comprising: a lecithin , MCT, bile salt, and water, in a four-component LMBW compn., their prepn. and applications in drug formulations.

IPCI A61K0009-08 [I]; A61K0009-00 [I]; A61K0047-14 [I]; A61K0047-54 [I]

IPCR A61K0009-08 [I]; A61K0009-00 [I]; A61K0047-14 [I]; A61K0047-54 [I]

CC 63-6 (Pharmaceuticals)

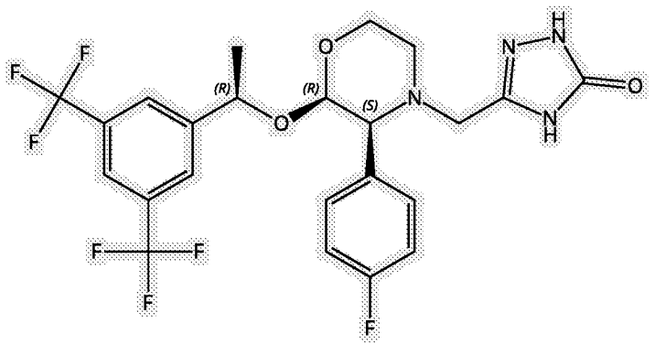
IT Bile salts
Egg yolk lecithins
Lecithins
Medium-chain glycerides
Polyoxyalkylenes
Sesame oil
Soya phosphatidylcholines
Soybean oil
Tocopherols
RL: MOA (Modifier or additive use); USES (Uses)
(aq. formulations for insol. drugs)

IT 52-21-1, Prednisolone Acetate 57-83-0, Progesterone, biological studies 59-92-7, Levodopa, biological studies 60-18-4, L-Tyrosine, biological studies 84-80-0, Phytonadione 501-36-0, Resveratrol 1951-25-3, Amiodarone 2078-54-8, Propofol 7553-56-2, Iodine, biological studies 7689-03-4, Camptothecin 12633-72-6, Amphotericin 15687-27-1, Ibuprofen 33069-62-4, Paclitaxel 59865-13-3, Cyclosporine 81103-11-9, Clarithromycin 84625-61-6, Itraconazole 100286-90-6, Irinotecan hydrochloride 169590-42-5, Celecoxib 170729-80-3, Aprepitant 171228-49-2, Posaconazole
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aq. formulations for insol. drugs)

IT 170729-80-3, Aprepitant
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aq. formulations for insol. drugs)

RN 170729-80-3 CAPLUS

CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
AU 2019231699 A1	AU 2019-231699	Register
AU 2019231699 B2	AU 2019-231699	Register
CA 3088017 A1	CA 2019-3088017	Register
CN 111867562 A	CN 2019-80017435	Register|Global Dossier
CN 111867562 B	CN 2019-80017435	Register|Global Dossier
EP 3761961 A1	EP 2019-764228	Register|Federated Reg.
JP 2021515048 T	JP 2020-570411	Register|Global Dossier
US 11541006 B2	US 2020-16993017	Register|Global Dossier
US 20200368159 A1	US 2020-16993017	Register|Global Dossier
WO 2019173526 A1	WO 2019-US21029	Register|Global Dossier

L5 ANSWER 18 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2019:1475315 CAPLUS Full-text
DOCUMENT NUMBER: 171:221789
TITLE: Method of administering emulsion formulations of an NK-1 receptor antagonist
INVENTOR(S): Ottoboni, Thomas B.; Quart, Barry D.
PATENT ASSIGNEE(S): Heron Therapeutics, Inc., USA
ULTIMATE OWNER: HERON THERAPEUTICS, INC.
ULTIMATE OWNER STANDARD: HERON THERAPEUTICS, INC.
SOURCE: U.S. Pat. Appl. Publ., 23pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

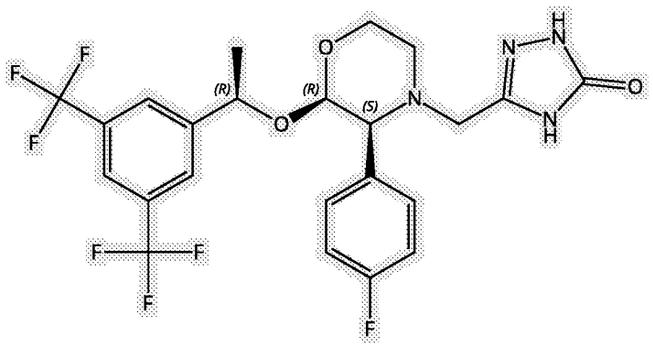
PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 20190231688	A1	20190801	US 2019-16261459		20190129
WO 2019152430	A1	20190808	WO 2019-US15708		20190129
AU 2019214872	A1	20200806	AU 2019-214872		20190129
EP 3746051	A1	20201209	EP 2019-705044		20190129
JP 2021512091	T	20210513	JP 2020-541556		20190129
PRIORITY APPLN. INFO.:			US 2018-62624050	P	20180130
			WO 2019-US15708	W	20190129

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
US 20190231688	A1	Alive	20230914
WO 2019152430	A1	Dead	20220929
AU 2019214872	A1	Dead	20230803
EP 3746051	A1	Dead	20211117
JP 2021512091	T	Alive	20210520

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASFORMULTNS 2019:1475315
AB Disclosed herein are methods of administering pharmaceutical formulations of a neurokinin-1 (NK-1) receptor antagonist to a subject in need of

treatment of emesis.
IPCI A61K0009-107 [I]; A61K0031-5377 [I]; A61K0009-00 [I]; A61K0047-24 [I];
A61K0031-573 [I]; A61K0047-44 [I]; A61K0047-10 [I]; A61K0047-12 [I];
A61K0047-26 [I]; A61K0031-496 [I]
IPCR A61K0009-107 [I]; A61K0009-00 [I]; A61K0031-496 [I]; A61K0031-5377 [I];
A61K0031-573 [I]; A61K0047-10 [I]; A61K0047-12 [I]; A61K0047-24 [I];
A61K0047-26 [I]; A61K0047-44 [I]
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1, 2
IT Alcohols
Egg yolk lecithins
Phospholipids
Soybean oil
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)
(method of administering emulsion formulations of NK-1 receptor
antagonist)
IT 2392-39-4, Dexamethasone sodium phosphate 147116-64-1, Ezlopitant
147116-67-4, Maropitant 170729-80-3, Aprepitant 290296-68-3,
Befetupitant 290297-26-6, Netupitant 334476-46-9, Vestipitant
414910-27-3, Casopitant 552292-08-7, Rolapitant 579475-18-6,
Orvepitant 860642-69-9, Ser-lopitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(method of administering emulsion formulations of NK-1 receptor
antagonist)
IT 170729-80-3, Aprepitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(method of administering emulsion formulations of NK-1 receptor
antagonist)
RN 170729-80-3 CAPLUS
CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phen
yl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX
NAME)



Absolute stereochemistry shown
Rotation (+)

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
AU 2019214872 A1	AU 2019-214872	Register
EP 3746051 A1	EP 2019-705044	Register|Federated Reg.
JP 2021512091 T	JP 2020-541556	Register|Global Dossier
US 20190231688 A1	US 2019-16261459	Register|Global Dossier
WO 2019152430 A1	WO 2019-US15708	Register|Global Dossier

L5 ANSWER 19 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2019:425605 CAPLUS Full-text
DOCUMENT NUMBER: 170:406568
TITLE: Aprepitant emulsion for treating nausea and vomiting after chemotherapy in tumor patient, and its preparation method and application
INVENTOR(S): Xu, Wendong; Tang, Shunzhi; Yuan, Cheng; Niu, Yawei;

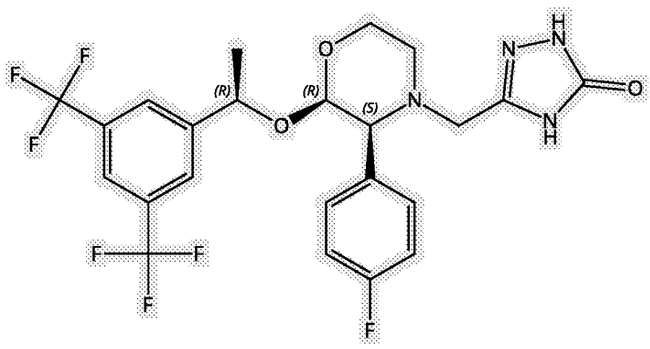
Fu, Yuping; Wang, Guocai; Guan, Weijian; Mou, Xiaonan; He, Jie; Li, Jirong; Yang, Yuqiong; Li, Yao
PATENT ASSIGNEE(S): Guangzhou Baiyunshan Hanfang Pharmaceutical Co., Ltd., Peop. Rep. China
ULTIMATE OWNER: GUANGZHOU BAIYUNSHAN PHARMACEUTICAL HOLDINGS CO., LTD.
ULTIMATE OWNER STANDARD: Guangzhou Baiyunshan Pharma
SOURCE: Faming Zhuanli Shenqing, 14pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 109432002	A	20190308	CN 2018-11587906	20181225

PRIORITY APPLN. INFO.: CN 2018-11587906 20181225
PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
CN 109432002	A	Dead	20220825

OTHER SOURCE(S): CASFORMULTNS 2019:425605
AB An aprepitant emulsion useful for reducing nausea and vomiting in the pre and post-chemotherapy of the tumor, improving immunity and nutritional support of the tumor patient, and reducing acute and delayed nausea and vomiting in high-dose cisplatin combined with high-dose sensitized cancer chemotherapy is provided. The aprepitant emulsion comprises the following components in mass %: 0.05-2.5 of aprepitant, 10-30 of oil phase solvent, 0.8-18 of emulsifier, 0.03-0.6 of stabilizer, 1-5 of isotonicity regulator, and further comprising a pH regulator, balance being purified water, where the pH of the emulsion is 5.5-8. The prepn. method comprises the following steps: (1) weighing the oil phase solvent, emulsifier and antioxidant, heating in a water bath, dissolving all the emulsifiers, and adding aprepitant and dissolving well to obtain an oil phase; (2) weighing stabilizer, isotonicity regulator, pH regulator, adding to purified water, and heating in water bath to obtain water phase; (3) slowly adding the oil phase to the water phase, shearing at high speed under stirring, adding the remaining purified water with high speed stirring to obtain colostrum; (4) subjecting obtained colostrum to microfluidization to obtain a final emulsion; and (5) filling the colostrum with nitrogen, sealing and sterilizing in a rotary sterilizing pot to obtain an aprepitant emulsion.
IPCI A61K0009-107; A61K0031-5377; A23L0033-10; A23P0010-00; A61P0001-08; A61P0035-00
IPCR A61K0009-107 [I]; A23L0033-10 [I]; A23P0010-00 [I]; A61K0031-5377 [I]; A61P0001-08 [I]; A61P0035-00 [I]
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1
IT Egg yolk lecithins
Fatty acids
Phosphatidylcholines
Phosphatidylglycerols
Soya lecithins
Tocopherols
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aprepitant emulsion for treating nausea and vomiting after chemotherapy in tumor patient, and its prepn. method and application)
IT 50-99-7, D-Glucose, biological studies 56-81-5, Glycerin, biological studies 69-65-8, D-Mannitol 112-80-1, Oleic acid, biological studies 143-19-1, Sodium oleate 7631-90-5, Sodium bisulfite 7647-14-5, Sodium chloride, biological studies 7681-57-4, Sodium metabisulfite 7772-98-7, Sodium thiosulfate 9005-65-6, Polysorbate 80 106392-12-5, Poloxamer 170729-80-3, Aprepitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aprepitant emulsion for treating nausea and vomiting after chemotherapy in tumor patient, and its prepn. method and application)
IT 170729-80-3, Aprepitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aprepitant emulsion for treating nausea and vomiting after chemotherapy in tumor patient, and its prepn. method and application)
RN 170729-80-3 CAPLUS
CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
CN 109432002 A	CN 2018-11587906	Register|Global Dossier

L5 ANSWER 20 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2019:340286 CAPLUS Full-text
DOCUMENT NUMBER: 170:348016
TITLE: Aprepitant intravenous emulsion for treating chemotherapy-induced nausea and vomiting, and its preparation method
INVENTOR(S): Yuan, Cheng; Xu, Wendong; Tang, Shunzhi; He, Jie; Niu, Yawei; Fu, Yuping; Wang, Guocai; Guan, Weijian; Mou, Xiaonan; Li, Yao
PATENT ASSIGNEE(S): Guangzhou Baiyunshan Hanfang Pharmaceutical Co., Ltd., Peop. Rep. China
ULTIMATE OWNER: GUANGZHOU BAIYUNSHAN PHARMACEUTICAL HOLDINGS CO., LTD.
ULTIMATE OWNER STANDARD: Guangzhou Baiyunshan Pharma
SOURCE: Faming Zhuanli Shenqing, 11pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 109364023	A	20190222	CN 2018-11588409	20181225

PRIORITY APPLN. INFO.: CN 2018-11588409 20181225
PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
CN 109364023	A	Transitional	20240222

OTHER SOURCE(S): CASFORMULTNS 2019:340286
AB The present invention relates to an i.v. emulsion contg. the following components by mass percentage: 0.05-3% of aprepitant, 5-30% of oil phase solvent, 1.2-18% of emulsifier, 0.03-0.6% of stabilizer, 1-5% of isotonicity adjusting agent, and 0.02-0.5% of antioxidant. The i.v. emulsion further contains a pH adjusting agent and water for injection, where the pH of the i.v. emulsion is 5.5-8.0. The i.v. emulsion has greatly improved the clin. safety, and is utilized for treating acute and delayed nausea and vomiting caused by high-dose cisplatin combined with high-dose sensitizing cancer chemotherapy and reducing nausea and vomiting in the early and middle stages of tumor chemotherapy.
IPCI A61K0009-107; A61K0047-24; A61K0047-12; A61K0031-5377; A61P0035-00; A61P0001-08
IPCR A61K0009-107 [I]; A61K0031-5377 [I]; A61K0047-12 [I]; A61K0047-24 [I]; A61P0001-08 [I]; A61P0035-00 [I]
CC 63-6 (Pharmaceuticals)
IT Castor oil

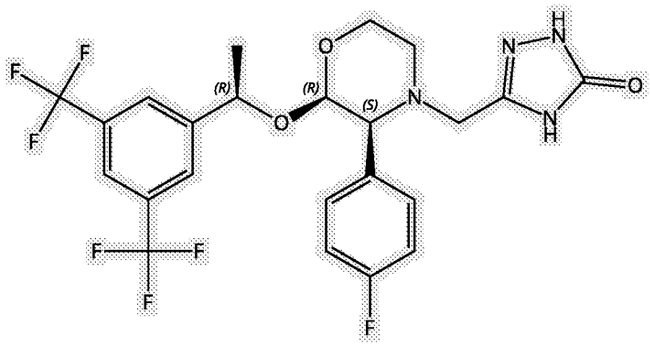
Egg yolk lecithins
Fish oil
Olive oil
Phosphatidylcholines
Phosphatidylglycerols
Soya phospholipids
Soybean oil
Teaseed oil
Tocopherols
RL: MOA (Modifier or additive use); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aprepitant i.v. emulsion for treating chemotherapy-induced nausea and vomiting, and its prepn. method)

IT 170729-80-3, Aprepitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aprepitant i.v. emulsion for treating chemotherapy-induced nausea and vomiting, and its prepn. method)

IT 170729-80-3, Aprepitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aprepitant i.v. emulsion for treating chemotherapy-induced nausea and vomiting, and its prepn. method)

RN 170729-80-3 CAPLUS

CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
CN 109364023 A	CN 2018-11588409	Register|Global Dossier

L5 ANSWER 21 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2018:2521745 CAPLUS Full-text
DOCUMENT NUMBER: 170:140265
TITLE: High stability aprepitant nano-emulsion and preparation method thereof
INVENTOR(S): Fu, Jifeng; Wang, Wenjuan; Guo, Jia; Zhang, Liancheng
PATENT ASSIGNEE(S): Beijing Ruiyue Biomedical Technology Co., Ltd., Peop. Rep. China
ULTIMATE OWNER: BEIJING RUIYUE BIOLOGY MEDICAL TECH
ULTIMATE OWNER STANDARD: BEIJING RUIYUE BIOLOGY MEDICAL TECH
SOURCE: Faming Zhuanli Shenqing, 9pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 109010272	A	20181218	CN 2018-11133738	20180927

PRIORITY APPLN. INFO.: CN 2018-11133738 20180927
PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
CN 109010272	A	Dead	20230323

OTHER SOURCE(S): CASFORMULTNS 2018:2521745

AB The invention discloses a nano-emulsion of aprepitant as shown in structure I and prepn. method thereof. The nano-emulsion is prepd. with the following components in percentage by wt.: aprepitant 0.05-1.5%, soybean oil 2-20%, egg yolk lecithin 5-20%, ethanol 0.5-5%, sodium oleate 0.05-2%, sucrose 2-10%, and water for injection 40-80%. The sodium oleate is added into the oil phase to rapidly stabilize the oil droplets when contacts with the aq. phase, thereby increasing the stability of the nano-emulsion.

IPCI A61K0009-107; A61K0047-12; A61K0047-44; A61K0047-24; A61K0047-10; A61K0047-26; A61K0031-5377; A61P0001-08

IPCR A61K0009-107 [I]; A61K0031-5377 [I]; A61K0047-10 [I]; A61K0047-12 [I]; A61K0047-24 [I]; A61K0047-26 [I]; A61K0047-44 [I]; A61P0001-08 [I]

CC 63-6 (Pharmaceuticals)

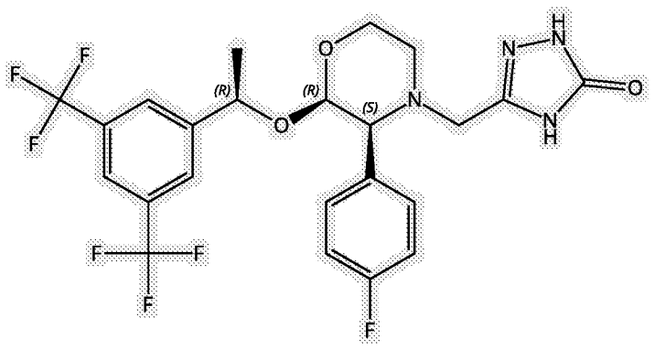
IT Egg yolk lecithins
Soybean oil
RL: MOA (Modifier or additive use); NANO (Nanomaterial); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(High stability aprepitant nano-emulsion and prepn. method thereof)

IT 170729-80-3, Aprepitant
RL: NANO (Nanomaterial); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(High stability aprepitant nano-emulsion and prepn. method thereof)

IT 170729-80-3, Aprepitant
RL: NANO (Nanomaterial); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(High stability aprepitant nano-emulsion and prepn. method thereof)

RN 170729-80-3 CAPLUS

CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
CN 109010272 A	CN 2018-11133738	Register|Global Dossier

L5 ANSWER 22 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2018:2521716 CAPLUS Full-text
DOCUMENT NUMBER: 170:154781
TITLE: Fat emulsion injection of aprepitant with improved stability for treating chemotherapy-induced nausea and vomiting
INVENTOR(S): Liu, Jie; Liu, Yun; Zhou, Lili
PATENT ASSIGNEE(S): Fubicheng (Shanghai) Pharmaceutical Technology Co.,

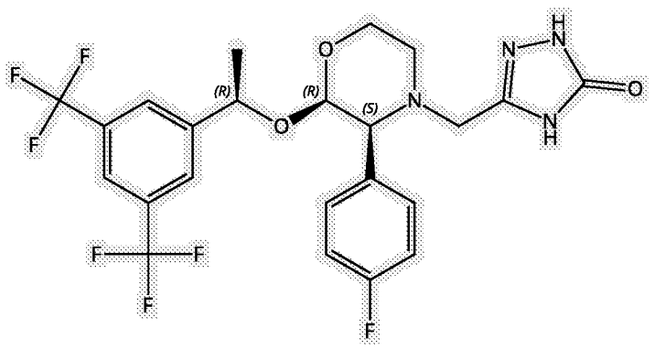
Ltd., Peop. Rep. China
ULTIMATE OWNER: FUBICHENG SHANGHAI MEDICINE TECH
ULTIMATE OWNER STANDARD: FUBICHENG SHANGHAI MEDICINE TECH
SOURCE: Faming Zhuanli Shenqing, 11pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 109010269	A	20181218	CN 2018-10979074	20180827
CN 109010269	B	20210420		

PRIORITY APPLN. INFO.: CN 2018-10979074 20180827
PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
CN 109010269	A	Alive	20201121
CN 109010269	B	Alive	20210430

OTHER SOURCE(S): CASFORMULTNS 2018:2521716
AB The title fat emulsion injection of aprepitant for treating chemotherapy-induced nausea and vomiting is prepd. from aprepitant, egg yolk lecithin , oil for injection (coconut oil, soybean oil, or olive oil), glycine, polyvinylpyrrolidone, water for injection, sodium oleate, and C1-5 short-chain alc. (ethanol or propanediol). The inventive prepn. has improved stability and reduced vascular irritation.
IPCI A61K0009-107; A61K0031-5377; A61K0047-18; A61K0047-32; A61K0031-439; A61K0009-08; A61P0001-08
IPCR A61K0009-107 [I]; A61K0009-08 [I]; A61K0031-439 [I]; A61K0031-5377 [I]; A61K0047-18 [I]; A61K0047-32 [I]; A61P0001-08 [I]
CC 63-6 (Pharmaceuticals)
IT Egg yolk lecithins
RL: MOA (Modifier or additive use); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(Lipoid E 80; fat emulsion injection of aprepitant with improved stability for treating chemotherapy-induced nausea and vomiting)
IT 170729-80-3, Aprepitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(fat emulsion injection of aprepitant with improved stability for treating chemotherapy-induced nausea and vomiting)
IT 170729-80-3, Aprepitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(fat emulsion injection of aprepitant with improved stability for treating chemotherapy-induced nausea and vomiting)
RN 170729-80-3 CAPLUS
CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
CN 109010269 A	CN 2018-10979074	Register|Global Dossier
CN 109010269 B	CN 2018-10979074	Register|Global Dossier

L5 ANSWER 23 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2018:1210583 CAPLUS Full-text
DOCUMENT NUMBER: 169:118657
TITLE: Novel formulations of aprepitant
INVENTOR(S): Titley, Paul Charlton
PATENT ASSIGNEE(S): N4 Pharma UK Limited, UK
ULTIMATE OWNER: N4 PHARMA UK; N4 PHARMA
ULTIMATE OWNER STANDARD: N4 PHARMA UK; N4 PHARMA
SOURCE: PCT Int. Appl., 85pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2018115888	A1	20180628	WO 2017-GB53864		20171221
PRIORITY APPLN. INFO.:			GB 2016-21867	A	20161221
			GB 2017-16293	A	20171005

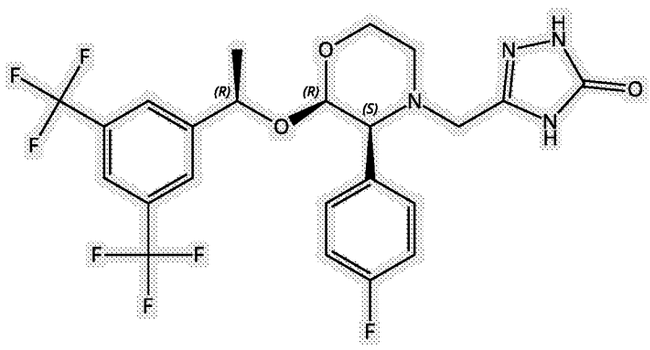
PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
WO 2018115888	A1	Dead	20210826

OTHER SOURCE(S): CASFORMULTNS 2018:1210583
AB The invention provides a pharmaceutical compn. which comprises: a first fraction comprising aprepitant; and a controlled-release fraction comprising aprepitant.
IPCI A61K0009-20 [I]; A61K0009-24 [I]; A61K0031-00 [I]
IPCR A61K0009-20 [I]; A61K0009-24 [I]; A61K0031-00 [I]
CC 63-1 (Pharmaceuticals)
IT Acrylic polymers
Activated charcoal
Alkali metal bicarbonates
Alkali metal carbonates
Carnauba wax
Fatty acids
Gelatins
Hydrogenated vegetable oils
Lecithins
Paraffin waxes
Polyoxyalkylenes
Polysaccharides
Shellac
Silica gel
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(novel formulations of aprepitant)
IT 50-02-2, Dexamethasone 50-07-7, Mitomycin C 50-18-0, Cyclophosphamide 50-35-1, Synovir 50-44-2, Mercaptopurine 50-69-1, Ribose 50-76-0, Dactinomycin 52-24-4, Thiotepa 53-03-2, Prednisone 55-86-7, Mechlorethamine hydrochloride 56-40-6, Glycine, biological studies 57-11-4, Stearic acid, biological studies 57-48-7, Fructose, biological studies 57-50-1, Sucrose, biological studies 57-88-5, Cholesterol, biological studies 59-23-4, Galactose, biological studies 61-90-5, Leucine, biological studies 63-42-3, Lactose 67-68-5, Sclerosol, biological studies 69-65-8, Mannitol 69-79-4, Maltose 70-00-8, Trifluridine 77-92-9, Citric acid, biological studies 79-41-4, biological studies 106-60-5, Aminolevulinic acid 112-92-5, Stearyl alcohol 127-07-1, Hydrea 134-62-3, OFF 143-67-9, Vinblastine sulfate 144-55-8, Sodium bicarbonate, biological studies 147-81-9, Arabinose 148-82-3, Alkeran 151-21-3, Sodium lauryl sulphate, biological studies 154-42-7, Tabloid 154-93-8, Carmustine 305-03-3, Ambochlorin 320-67-2, Azacitidine 366-70-1, Procarbazine hydrochloride 555-44-2, Glyceryl tripalmitate 557-04-0, Magnesium stearate 585-88-6, Maltitol 595-33-5, Megestrol acetate 1323-83-7, Glyceryl distearate 1327-43-1, Aluminum Magnesium silicon oxide 1327-53-3, Arsenic Trioxide 1492-18-8, Leucovorin calcium 2068-78-2, Vincristine sulfate 2068-78-2D, Vincristine sulfate, liposomes 2353-33-5, Dacogen

2921-88-2, Cyfos 3543-75-7, Treanda 4105-38-8, Uridine triacetate 4342-03-4, Dacarbazine 7447-40-7, Potassium chloride, biological studies 7447-41-8, Lithium chloride, biological studies 7487-88-9, Magnesium sulphate, biological studies 7631-86-9, Silica, biological studies 7647-14-5, Sodium chloride, biological studies 7757-82-6, Sodium sulphate, biological studies 7778-80-5, Potassium sulphate, biological studies 7786-30-3, Magnesium chloride, biological studies 9000-30-0, Guar gum 9000-69-5, Pectin 9000-92-4, Amylase 9003-39-8, Polyvinylpyrrolidone 9004-32-4, Carboxymethylcellulose 9004-34-6, Cellulose, biological studies 9004-34-6D, Cellulose, ethers 9004-35-7 9004-38-0, Cellulose acetate phthalate 9004-57-3, Ethyl cellulose 9004-62-0, Hydroxyethylcellulose 9004-64-2, Hydroxypropylcellulose 9004-65-3, Hydroxypropylmethylcellulose 9004-67-5, Methylcellulose 9005-25-8, Starch, biological studies 9005-32-7, Alginic acid 9005-38-3, Sodium alginate 9032-42-2, Hydroxyethyl-methylcellulose 9050-04-8 9050-31-1, Hydroxypropylmethylcellulose phthalate 9063-38-1, Sodium starch glycolate 10377-48-7, Lithium sulphate 11056-06-7, Bleomycin 11138-66-2, Xanthan gum 13010-47-4, Lomustine 13311-84-7, Flutamide 14807-96-6, Talc, biological studies 18641-57-1 19171-19-8, Pomalidomide 19767-45-4, Mesna 20830-81-3, Rubidomycin 23214-92-8, Doxil 24584-09-6, Totect 25086-15-1, Methacrylic acid-methyl methacrylate co-polymer 25212-88-8, Methacrylic acid-ethyl acrylate copolymer 25316-40-9, Doxorubicin hydrochloride 25322-68-3, Polyethylene glycol 26100-51-6, Polylactic acid 26124-68-5, Polyglycolic acid 26833-87-4, Omacetaxine mepesuccinate 31566-31-1, Glyceryl monostearate 33419-42-0, Etoposide 37380-42-0, Amberlite XAD 4 37380-43-1, Amberlite XAD 7 41575-94-4, Carboplatin 50935-57-4, Methyl vinyl ether-maleic acid copolymer ethyl ester 53237-50-6 54182-62-6, Polacrilin potassium 54578-91-5, Methyl vinyl ether-maleic acid copolymer butyl ester 56038-13-2, Sucralose 56390-09-1, Ellence 57248-88-1, Aredia 57852-57-0, Idamycin 61825-94-3, Eloxatin 64519-82-0, Isomalt 70476-82-3, Mitoxantrone hydrochloride 70535-77-2, Hydroxypropylmethylcellulose acetate succinate 74381-53-6, Leuprolide acetate 74811-65-7, Croscarmellose sodium 75607-67-9, Fludara 82640-04-8, Evista 83712-60-1, Defibrotide Sodium 84449-90-1, Keoxifene 85622-93-1, Methazolastone 89778-26-7, Fareston 90357-06-5, Bicalutamide 95058-81-4, Gemcitabine 97682-44-5, Irinotecan 98530-12-2, Interferon Alfa-2b 99011-02-6, Aldara 99614-01-4, Ondansetron hydrochloride 100286-90-6, Camptosar 100286-90-6D, Irinotecan hydrochloride, liposomes 104219-63-8, Amberlite XAD 16 108736-35-2, Somatuline Depot 110942-02-4, Aldesleukin 112809-51-5, Femara 114899-77-3, Trabectedin 114977-28-5, Docetaxel 117091-64-2, Etopophos 118072-93-8, Zoledronic acid 119413-54-6, Hycamtin 120511-73-1, Anastrozole 121181-53-1, Filgrastim 122111-03-9, Gemcitabine hydrochloride 122312-54-3 123119-31-3 123318-82-1, Clofarabine 125317-39-7, Navelbine 127984-74-1, Lanreotide acetate 128517-07-7, Istodax 129453-61-8, Faslodex 130167-69-0, Oncaspar 134774-45-1, Elitek 135729-62-3, Palonosetron hydrochloride 145781-92-6, Goserelin acetate 146464-95-1, Folotyn 148618-33-1, Ambersorb 572 148879-45-2, Ambersorb 563 149003-01-0, Dexrazoxane hydrochloride 149647-78-9, Vorinostat 150399-23-8, Alimta 153559-49-0, Bexarotene 154229-18-2, Abiraterone Acetate 154361-50-9, Capecitabine 159351-69-6, Everolimus 162394-19-6, Kepivance 162635-04-3, Temsirolimus 170729-80-3, Aprepitant 173146-27-5, Denileukin Diftitox 179324-69-7, Bortezomib 180288-69-1, Herceptin 183133-96-2, Cabazitaxel 183204-72-0, Tipiracil hydrochloride 183319-69-9, Erlotinib hydrochloride 184475-35-2, Gefitinib 191732-72-6, Lenalidomide 192391-48-3, Bexxar 205923-56-4, Cetuximab 206181-63-7, Ibritumomab Tiuxetan 208921-02-2, Tositumomab 208921-02-2D, Tositumomab, Iodine I-131 214766-78-6, Degarelix 215647-85-1, Peginterferon Alfa-2b 216503-57-0, Alemtuzumab 216974-75-3, Avastin 219989-84-1, Ixabepilone 220127-57-1, Gleevec 220578-59-6, Gemtuzumab 290297-26-6, Akynzeo 302962-49-8, Dasatinib 319460-85-0, Axitinib 339177-26-3, Panitumumab 341031-54-7, Sunitinib malate 380610-27-5, Perjeta 380843-75-4, Bosulif 388082-77-7, Lapatinib ditosylate 400046-53-9, Ozogamicin 404950-80-7, Farydak 417716-92-8, Lenvima 441045-17-6, Eribulin mesylate 443913-73-3, Vandetanib 477202-00-9, Ipilimumab 496775-62-3, Eltrombopag Olamine 541502-14-1, Siltuximab 571190-30-2, Ibrance 615258-40-7, Denosumab 635702-64-6, Pazopanib hydrochloride 641571-10-0, Nilotinib 679818-59-8, Arzerra 733030-01-8, Lonsurf 755037-03-7, Regorafenib 763113-22-0, Lynparza 843613-19-4, Ambersorb 348F 849217-68-1,

Cabometyx 850140-72-6, Gilotrif 850140-73-7, Afatinib dimaleate
853426-35-4, Blinatumomab 857890-39-2, Lenvatinib mesylate
858102-79-1, Rolapitant hydrochloride 866323-14-0, Beleodaq
868540-17-4, Carfilzomib 870281-82-6, Idelalisib 871700-17-3, Mekinist
877399-52-5, Crizotinib 879085-55-9, Erivedge 906805-06-9, Necitumumab
910046-32-1, Gardasil 912337-47-4, Cervarix 914088-09-8, Adcetris
915087-33-1, Enzalutamide 915296-00-3, Elotuzumab 917381-47-6,
Provenge 918504-65-1, Vemurafenib 930113-49-8, CAPOX
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(novel formulations of aprepitant)
IT 170729-80-3, Aprepitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(novel formulations of aprepitant)
RN 170729-80-3 CAPLUS
CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phen
yl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX
NAME)



Absolute stereochemistry shown
Rotation (+)

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
WO 2018115888 A1	WO 2017-GB53864	Register|Global Dossier

L5 ANSWER 24 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2017:1728289 CAPLUS Full-text
DOCUMENT NUMBER: 168:9512
TITLE: Nanocrystal composition for improving oral absorption of insoluble drug
INVENTOR(S): Liu, Yan; Li, Xueping; Li, Xinru; Zhou, Yanxia
PATENT ASSIGNEE(S): Peking University, Peop. Rep. China
SOURCE: Faming Zhuanli Shenqing, 11pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 107303272	A	20171031	CN 2016-10239333	20160418

PRIORITY APPLN. INFO.: CN 2016-10239333 20160418
PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
CN 107303272	A	Dead	20220527

OTHER SOURCE(S): CASFORMULTNS 2017:1728289
AB The title compn. is composed of an insol. drug, a stabilizer, the ligand of the specific receptor expressed by intestinal epithelial cell and/or substrate of transporter and optional pharmaceutically acceptable auxiliary, and is prepd. by prepg. into a suspension and lyophilizing. The expt. proves that the compn. can remarkably improve the oral

absorption of the insol. drug so as to provide the prepn. strategy for insol. drug oral administration.

IPCI A61K0009-10; A61K0009-19; A61K0047-10; A61K0047-42; A61K0047-22; A61K0047-26; A61K0047-18; A61K0047-24; A61K0047-38; A61K0047-32; A61K0031-4745; A61K0031-337; A61K0031-7048; A61K0031-436; A61K0031-5377; A61K0031-357

IPCR A61K0009-10 [I]; A61K0009-19 [I]; A61K0031-337 [I]; A61K0031-357 [I]; A61K0031-436 [I]; A61K0031-4745 [I]; A61K0031-5377 [I]; A61K0031-7048 [I]; A61K0047-10 [I]; A61K0047-18 [I]; A61K0047-22 [I]; A61K0047-24 [I]; A61K0047-26 [I]; A61K0047-32 [I]; A61K0047-38 [I]; A61K0047-42 [I]

CC 63-6 (Pharmaceuticals)

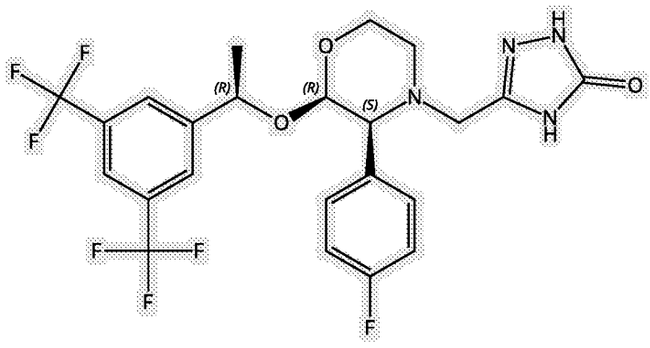
IT Amino acids
Dipeptides
Ethoxylated hydrogenated castor oil
Lecithins
Polyoxyalkylenes
Soya phospholipids
Transferrins
Tripeptides
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nanocrystal compn. for improving oral absorption of insol. drug)

IT 50-02-2, Dexamethasone 50-04-4, Cortisone acetate 426-13-1, Fluorometholone 458-37-7, Curcumin 15687-27-1, Ibuprofen 19685-09-7, 10-Hydroxycamptothecin 22888-70-6, Silibinin 25316-40-9, Adriamycin 29767-20-2, Teniposide 33069-62-4, Paclitaxel 33419-42-0, Etoposide 34368-04-2, Dobutamine 35354-74-6, Honokiol 49562-28-9, Fenofibrate 51333-22-3, Budesonide 59865-13-3, Cyclosporin A 65666-07-1, Silymarin 80474-14-2, Fluticasone propionate 84625-61-6, Itraconazole 91421-42-0, 9-Nitrocamptothecin 104987-11-3, Tacrolimus 114977-28-5, Docetaxel 170729-80-3, Aprepitant
RL: NANO (Nanomaterial); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nanocrystal compn. for improving oral absorption of insol. drug)

IT 170729-80-3, Aprepitant
RL: NANO (Nanomaterial); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nanocrystal compn. for improving oral absorption of insol. drug)

RN 170729-80-3 CAPLUS

CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



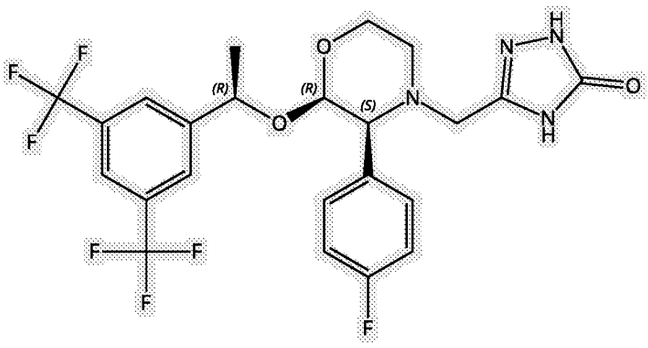
Absolute stereochemistry shown
Rotation (+)

OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
CN 107303272 A	CN 2016-10239333	Register|Global Dossier

L5 ANSWER 25 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2017:1554024 CAPLUS Full-text
DOCUMENT NUMBER: 168:18112
TITLE: Biorelevant Drug Solubility Enhancement Modeled by a Linear Solvation Energy Relationship
AUTHOR(S): Niederquell, Andreas; Kuentz, Martin
CORPORATE SOURCE: Institute of Pharma Technology, University of Applied Sciences and Arts Northwestern Switzerland, Muttenz, 4132, Switz.
SOURCE: Journal of Pharmaceutical Sciences (Philadelphia, PA, United States) (2018), 107(1), 503-506
CODEN: JPMSAE; ISSN: 0022-3549
DIGITAL OBJECT ID: 10.1016/j.xphs.2017.08.017
PUBLISHER: Elsevier Inc.
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
AB It is for the pharmaceutical sciences of vital importance to understand how drugs are solubilized in biorelevant media. However, the complexity of fasted state simulated intestinal fluid (FaSSIF) has so far hampered adequate soly. modeling. The present study focuses on apparently neutral compds. at physiol. pH and a linear free energy relationship is introduced for biorelevant drug solubilization. Based on literature data of 40 compds., the Abraham solvation descriptors were calcd. from chem. structure to then predict the ratio of soly. enhancement log(SE) in FaSSIF compared to aq. buffer soly. at pH 6.5. A suitable model was obtained with R2 of 0.810 and notable were esp. the pos. effect of McGowan's characteristic vol. and the neg. effect of drug basicity. A neg. influence on log(SE) was further evidenced for dipolarity/polarizability and for the excess molar refraction descriptor. A pos. solubilization effect was obtained for drug acidity and hence the tendency for proton donation, which was likely due to the different proton-accepting moieties of taurocholic acid and lecithin that are both present in the mixed colloids of FaSSIF. Overall, an improved understanding was achieved regarding the mol. features that are driving drug solubilization in biorelevant media.
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1
IT Lecithins
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(biorelevant drug soly. enhancement modeled by a linear solvation energy relationship)
IT 50-02-2, Dexamethasone 50-28-2, Estra-1,3,5(10)-triene-3,17-diol (17β)-, biological studies 52-01-7, Spironolactone 53-03-2, Prednisone 53-16-7, Estrone, biological studies 57-41-0, Phenytoin 57-83-0, Progesterone, biological studies 58-22-0, Testosterone 58-32-2, Dipyridamole 58-94-6, Chlorothiazide 81-24-3, Taurocholic acid 81-81-2, Warfarin 84-17-3, Dienestrol 126-07-8, Griseofulvin 298-46-4, Carbamazepine 439-14-5, Diazepam 846-49-1, Lorazepam 17230-88-5 23288-49-5, Probucol 39562-70-4, Nitrendipine 49562-28-9, Fenofibrate 51803-78-2, Nimesulide 54965-21-8, Albendazole 55268-74-1 59865-13-3, Cyclosporine 65646-68-6, Fenretinide 70288-86-7, Ivermectin 72509-76-3 73963-72-1, Cilostazole 75330-75-5, Lovastatin 95233-18-4, Atovaquone 103577-45-3, Lansoprazole 124423-84-3, Panadiplon 138402-11-6 154598-52-4 161814-49-9, Amprenavir 162011-90-7, Rofecoxib 169590-42-5, Celecoxib 170729-80-3, Aprepitant 192725-17-0, Lopinavir 262352-17-0, Torcetrapib
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(biorelevant drug soly. enhancement modeled by a linear solvation energy relationship)
IT 170729-80-3, Aprepitant
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(biorelevant drug soly. enhancement modeled by a linear solvation energy relationship)
RN 170729-80-3 CAPLUS
CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

OS.CITING REF COUNT: 19 THERE ARE 19 CAPLUS RECORDS THAT CITE THIS RECORD (19 CITINGS)
REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 26 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2017:1232902 CAPLUS Full-text
DOCUMENT NUMBER: 167:591636
TITLE: Influence of Physiological Gastrointestinal Surfactant Ratio on the Equilibrium Solubility of BCS Class II Drugs Investigated Using a Four Component Mixture Design
AUTHOR(S): Zhou, Zhou; Dunn, Claire; Khadra, Ibrahim; Wilson, Clive G.; Halbert, Gavin W.
CORPORATE SOURCE: Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow, G4 0RE, UK
SOURCE: Molecular Pharmaceutics (2017), 14(12), 4132-4144
CODEN: MPOHBP; ISSN: 1543-8384
DIGITAL OBJECT ID: 10.1021/acs.molpharmaceut.7b00354
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English

AB The absorption of poorly water-sol. drugs is influenced by the luminal gastrointestinal fluid content and compn. which controls soly. Simulated intestinal fluids have been introduced into dissoln. testing including endogenous amphiphiles and digested lipids at physiol. levels; however, in vivo individual variation exists in the concns. of these components, which will alter drug absorption through an effect on soly. The use of a factorial design of expt. and varying media by introducing different levels of bile, lecithin and digested lipids has been previously reported, but here we investigate the soly. variation of poorly-sol. drugs through more complex biorelevant amphiphile interactions. A four component mixt. design was conducted to understand the solubilization capacity and interactions of bile salt, lecithin, oleate and monoglyceride with a const. total concn. (11.7 mM) but varying molar ratios. The equil. soly. of seven low soly. acidic (zafirlukast), basic (aprepitant, carvedilol) and neutral (fenofibrate, felodipine, griseofulvin and spironolactone) drugs was investigated. Soly. results are comparable with literature values and also our own previously published design of expt. studies. Results indicate that solubilization is not a sum accumulation of individual amphiphile concns., but a drug specific effect through interactions of mixed amphiphile compns. with the drug. This is probably due to a combined interaction of drug characteristics for example lipophilicity, mol. shape and ionization with amphiphile components, which can generate specific drug-micelle affinities. The proportion of each component can have a remarkable influence on soly. with in some cases the highest and lowest points close to each other. A single point soly. measurement in a fixed compn. simulated media or human intestinal fluid sample will therefore provide a value without knowledge of the surrounding soly. topog. meaning that

variability may be overlooked. This study has demonstrated how the amphiphile ratios influence drug soly. and highlights the importance of the envelope of physiol. variation when simulating in vivo drug behavior.

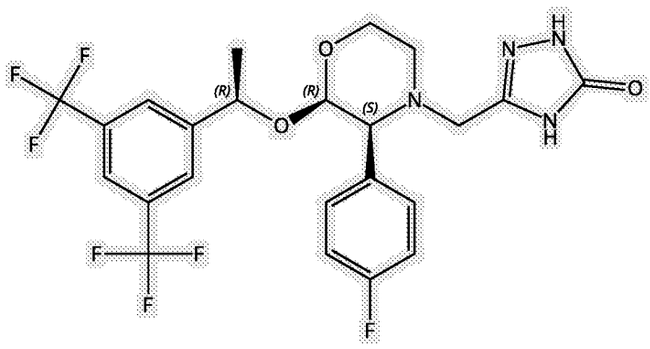
CC 63-6 (Pharmaceuticals)

IT 52-01-7, Spironolactone 126-07-8, Griseofulvin 49562-28-9, Fenofibrate 72509-76-3, Felodipine 72956-09-3, Carvedilol 107753-78-6, Zafirlukast 170729-80-3, Aprepitant
RL: PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(influence of physiol. gastrointestinal surfactant ratio on equil. soly. of BCS class II drugs investigated using a four component mixt. design)

IT 170729-80-3, Aprepitant
RL: PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(influence of physiol. gastrointestinal surfactant ratio on equil. soly. of BCS class II drugs investigated using a four component mixt. design)

RN 170729-80-3 CAPLUS

CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

OS.CITING REF COUNT: 28 THERE ARE 28 CAPLUS RECORDS THAT CITE THIS RECORD (28 CITINGS)

REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 27 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN

ACCESSION NUMBER: 2016:2157637 CAPLUS Full-text

DOCUMENT NUMBER: 166:118691

TITLE: Cosmeceutical compositions comprising polyalkylene glycols

INVENTOR(S): Schmaus, Gerhard; Lange, Sabine

PATENT ASSIGNEE(S): Symrise AG, Germany

ULTIMATE OWNER: SYMRISE AG

ULTIMATE OWNER STANDARD: Symrise

SOURCE: PCT Int. Appl., 56pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2016207084	A1	20161229	WO 2016-EP64109	20160619
EP 3108941	A1	20161228	EP 2015-173373	20150623
EP 3108941	B1	20180509		
KR 2018015265	A	20180212	KR 2018-7002058	20160619
KR 2117171	B1	20200601		
MX 2017016226	A	20180223	MX 2017-16226	20160619

CN 107847772	A	20180327	CN 2016-80045857		20160619
CN 107847772	B	20220104			
JP 2018518496	T	20180712	JP 2017-565942		20160619
JP 6945458	B2	20211006			
BR 112017027546	A2	20180821	BR 2017-112017027546		20160619
BR 112017027546	B1	20220426			
IN 201717044256	A	20180105	IN 2017-17044256		20171208
US 20180185301	A1	20180705	US 2017-15736494		20171214

PRIORITY APPLN. INFO.: EP 2015-173373 A 20150623
WO 2016-EP64109 W 20160619

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
WO 2016207084	A1	Dead	20201201
EP 3108941	A1	Indeterminate	20201106
EP 3108941	B1	Indeterminate	20201107
KR 2018015265	A	Alive	20201121
KR 2117171	B1	Alive	20201121
MX 2017016226	A	Alive	20201121
CN 107847772	A	Alive	20201121
CN 107847772	B	Alive	20220120
JP 2018518496	T	Alive	20201120
JP 6945458	B2	Alive	20211118
BR 112017027546	A2	Alive	20220519
BR 112017027546	B1	Alive	20220519
US 20180185301	A1	Dead	20220818

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OTHER SOURCE(S): CASFORMULTNS 2016:2157637

AB Suggested are compns. comprising or consisting of specific polyalkylene glycol deriv. as pharmaceutical actives for preventing, treating and/or curing itchy conditions of human skin and scalp, and/or providing a PAR-2 antagonistic effect to human skin and scalp.

IPCI A61Q0019-00 [I]; A61Q0005-00 [I]; A61Q0005-12 [I]; A61Q0017-04 [I]; A61Q0019-02 [I]; A61Q0015-00 [I]; A61K0008-39 [I]; A61K0008-33 [I]; A61K0031-08 [I]; A61K0031-25 [I]; A61P0017-04 [I]

IPCR A61K0008-33 [I]; A61Q0019-00 [I]; A61K0008-39 [I]; A61K0031-08 [I]; A61K0031-25 [I]; A61P0017-04 [I]; A61Q0005-00 [I]; A61Q0005-12 [I]; A61Q0015-00 [I]; A61Q0017-04 [I]; A61Q0019-02 [I]

CC 62-4 (Essential Oils and Cosmetics)
Section cross-reference(s): 63

IT Amino acids
Cannabinoids
Carbohydrates
Ceramides
Collagens
Corticosteroids
Disaccharides
Elastins
Glycosphingolipids
Hydroxy fatty acids
Hydroxycarboxylic acids
Lanolin
Lecithins
Oligosaccharides
Petrolatum
Phytosterols
Polyoxyalkylenes
Pyrazoles
Steroids
Tocopherols
RL: COS (Cosmetic use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cosmeceutical compns. comprising polyalkylene glycols)

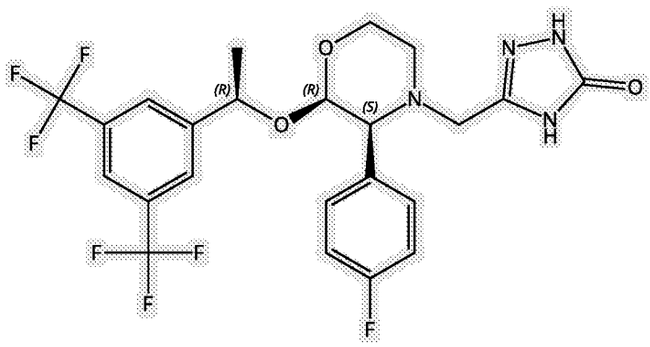
IT 50-02-2 50-21-5, biological studies 50-23-7 50-33-9, biological studies 50-78-2 50-99-7, D-Glucose, biological studies 53-06-5 53-86-1 56-81-5, 1,2,3-Propanetriol, biological studies 57-13-6, Urea, biological studies 57-48-7, D-Fructose, biological studies 57-55-6, 1,2-Propanediol, biological studies 57-88-5, Cholest-5-en-3-ol (3β)-, biological studies 58-95-7 59-23-4, D-Galactose, biological studies 61-68-7 63-42-3 69-46-5 72-17-3 77-52-1 77-92-9, biological studies 81-13-0 83-43-2 89-78-1 89-79-2 97-59-6 98-52-2 104-98-3 124-04-9D, Hexanedioic acid, acyl derivs.

129-20-4 312-93-6 472-15-1 502-65-8, ψ,ψ-Carotene 515-69-5
520-36-5 530-78-9 544-31-0 552-94-3 555-66-8 578-74-5 644-62-2
873-94-9 1117-77-7 1117-86-8, 1,2-Octanediol 1405-86-3, Glycyrrhizin
1406-18-4, Vitamin E 2304-80-5 3458-28-4, D-Mannose 3804-01-1
4394-00-7 5343-92-0, 1,2-Pentanediol 6915-15-7 6920-22-5,
1,2-Hexanediol 9004-61-9, Hyaluronic acid 9007-28-7 9012-76-4,
Chitosan 9041-22-9, β-D-Glucan 13539-59-8 13609-67-1
15307-86-5 15687-27-1 22204-53-1 24938-91-8 26171-23-3
27113-22-0 30748-29-9 34645-84-6 36322-90-4 36945-98-9
38194-50-2 41736-92-9 51115-67-4 51234-28-7 53254-77-6
53597-27-6 55965-23-6 58253-27-3, Gingerol 58749-22-7 59804-37-4
59870-68-7 61723-78-2 63187-91-7 74563-64-7 77341-67-4
106729-72-0 108766-16-1 110483-07-3 170729-80-3
185740-18-5 185915-25-7 189128-20-9 207792-35-6 211184-47-3
220621-22-7 381224-15-3 506412-91-5 521981-60-2 637336-79-9
697235-49-7 857557-19-8 1122460-01-8
RL: COS (Cosmetic use); THU (Therapeutic use); BIOL (Biological study);
USES (Uses)
(cosmeceutical compns. comprising polyalkylene glycols)

IT 170729-80-3
RL: COS (Cosmetic use); THU (Therapeutic use); BIOL (Biological study);
USES (Uses)
(cosmeceutical compns. comprising polyalkylene glycols)

RN 170729-80-3 CAPLUS

CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
BR 112017027546 A2	BR 2017-112017027546	Register
BR 112017027546 B1	BR 2017-112017027546	Register
CN 107847772 A	CN 2016-80045857	Register|Global Dossier
CN 107847772 B	CN 2016-80045857	Register|Global Dossier
EP 3108941 A1	EP 2015-173373	Register|Federated Reg.
EP 3108941 B1	EP 2015-173373	Register|Federated Reg.
IN 201717044256 A	IN 2017-17044256	Register
JP 2018518496 T	JP 2017-565942	Register|Global Dossier
JP 6945458 B2	JP 2017-565942	Register|Global Dossier
KR 2018015265 A	KR 2018-7002058	Register|Global Dossier
KR 2117171 B1	KR 2018-7002058	Register|Global Dossier
MX 2017016226 A	MX 2017-16226	Register
US 20180185301 A1	US 2017-15736494	Register|Global Dossier
WO 2016207084 A1	WO 2016-EP64109	Register|Global Dossier

L5 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2016:2152998 CAPLUS Full-text

DOCUMENT NUMBER: 166:112176
TITLE: Cosmeceutical compositions comprising polyalkylene glycols
INVENTOR(S): Schmaus, Gerhard; Lange, Sabine
PATENT ASSIGNEE(S): Symrise AG, Germany
ULTIMATE OWNER: SYMRISE AG
ULTIMATE OWNER STANDARD: Symrise
SOURCE: Eur. Pat. Appl., 46pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 3108941	A1	20161228	EP 2015-173373	20150623
EP 3108941	B1	20180509		
WO 2016207084	A1	20161229	WO 2016-EP64109	20160619
KR 2018015265	A	20180212	KR 2018-7002058	20160619
KR 2117171	B1	20200601		
MX 2017016226	A	20180223	MX 2017-16226	20160619
CN 107847772	A	20180327	CN 2016-80045857	20160619
CN 107847772	B	20220104		
JP 2018518496	T	20180712	JP 2017-565942	20160619
JP 6945458	B2	20211006		
BR 112017027546	A2	20180821	BR 2017-112017027546	20160619
BR 112017027546	B1	20220426		
IN 201717044256	A	20180105	IN 2017-17044256	20171208
US 20180185301	A1	20180705	US 2017-15736494	20171214

PRIORITY APPLN. INFO.:
EP 2015-173373 A 20150623
WO 2016-EP64109 W 20160619

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
EP 3108941	A1	Indeterminate	20201106
EP 3108941	B1	Indeterminate	20201107
WO 2016207084	A1	Dead	20201201
KR 2018015265	A	Alive	20201121
KR 2117171	B1	Alive	20201121
MX 2017016226	A	Alive	20201121
CN 107847772	A	Alive	20201121
CN 107847772	B	Alive	20220120
JP 2018518496	T	Alive	20201120
JP 6945458	B2	Alive	20211118
BR 112017027546	A2	Alive	20220519
BR 112017027546	B1	Alive	20220519
US 20180185301	A1	Dead	20220818

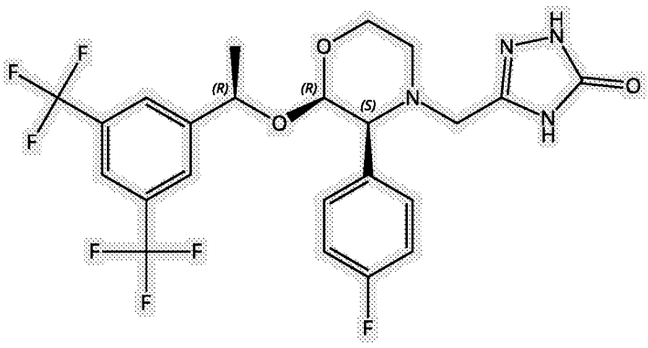
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASFORMULTNS 2016:2152998
AB Suggested are compns. comprising or consisting of specific polyalkylene glycol deriv. as pharmaceutical actives for preventing, treating and/or curing itchy conditions of human skin and scalp, and/or providing a PAR-2 antagonistic effect to human skin and scalp.
IPCI A61Q0019-00 [I]; A61Q0005-00 [I]; A61Q0005-12 [I]; A61Q0017-04 [I]; A61Q0019-02 [I]; A61Q0015-00 [I]; A61K0008-39 [I]; A61K0008-33 [I]; A61K0031-08 [I]; A61K0031-25 [I]; A61P0017-04 [I]
IPCR A61Q0019-00 [I]; A61K0008-33 [I]; A61K0008-39 [I]; A61K0031-08 [I]; A61K0031-25 [I]; A61P0017-04 [I]; A61Q0005-00 [I]; A61Q0005-12 [I]; A61Q0015-00 [I]; A61Q0017-04 [I]; A61Q0019-02 [I]
CC 62-4 (Essential Oils and Cosmetics)
Section cross-reference(s): 63
IT Amino acids
Cannabinoids
Carbohydrates
Ceramides
Collagens
Corticosteroids
Disaccharides
Elastins
Glycosphingolipids
Hydroxy fatty acids
Hydroxycarboxylic acids

Lanolin
Lecithins
Oligosaccharides
Petrolatum
Phytosterols
Polyoxyalkylenes
Pyrazoles
Steroids
Tocopherols
RL: COS (Cosmetic use); THU (Therapeutic use); BIOL (Biological study);
USES (Uses)
(cosmeceutical compns. comprising polyalkylene glycols)

IT 50-02-2, Dexamethasone 50-21-5, Lactic acid, biological studies
50-23-7, Hydrocortisone 50-33-9, Phenylbutazone, biological studies
50-78-2, Aspirin 50-99-7, D-Glucose, biological studies 53-06-5,
Cortisone 53-86-1, Indomethacin 56-81-5, Glycerol, biological studies
57-13-6, Urea, biological studies 57-48-7, D-Fructose, biological
studies 57-55-6, Propylene glycol, biological studies 57-88-5,
Cholesterol, biological studies 58-95-7, Tocopheryl acetate 59-23-4,
D-Galactose, biological studies 61-68-7, Mefenamic acid 63-42-3,
Lactose 69-46-5, Solprin 72-17-3, Sodium lactate 77-52-1, Ursolic
acid 77-92-9, Citric acid, biological studies 81-13-0 83-43-2,
Methylprednisolone 89-78-1, Menthol 89-79-2 97-59-6 98-52-2
104-98-3 124-04-9D, Adipic acid, acyl derivs. 129-20-4,
Oxyphenylbutazone 312-93-6, Dexamethasone phosphate 472-15-1, Betulic
acid 502-65-8, ψ,ψ-Carotene 515-69-5, α-Bisabolol
520-36-5, Apigenin 530-78-9, Flufenamic acid 544-31-0, N-Palmitoyl
Ethanolamine 552-94-3, Disalcid 555-66-8 578-74-5 629-54-9,
Hexadecanamide 644-62-2, Meclofenamic acid 873-94-9 1117-77-7
1117-86-8, 1,2-Octanediol 1405-86-3, Glycyrrhizin 1406-18-4, Vitamin E
2304-80-5 3458-28-4, D-Mannose 3804-01-1 4394-00-7, Niflumic acid
5343-92-0, 1,2-Pentanediol 6915-15-7, Malic acid 6920-22-5,
1,2-Hexanediol 9004-61-9, Hyaluronic acid 9007-28-7, Chondroitin
sulfate 9012-76-4, Chitosan 9041-22-9, β-Glucan 13539-59-8
13609-67-1, Hydrocortisone 17-butyrate 15307-86-5, Diclofenac
15687-27-1, Ibuprofen 22204-53-1, Naproxen 24938-91-8, Polyethylene
glycol Tridecyl ether 26171-23-3, Tolmetin 27113-22-0 30748-29-9,
Feprazone 34645-84-6, Fenclofenac 36322-90-4, Piroxicam 36945-98-9,
Icilin 38194-50-2, Sulindac 41736-92-9 51115-67-4,
2-Isopropyl-N-2,3-trimethylbutanamide 51234-28-7, Benoxaprofen
53254-77-6 53597-27-6, Fendosal 55965-23-6 58253-27-3, Gingerol
58749-22-7 59804-37-4, Tenoxicam 59870-68-7 61723-78-2 63187-91-7
74563-64-7 77341-67-4 106729-72-0 108766-16-1 170729-80-3
185740-18-5 185915-25-7, L-Menthyl lactate 189128-20-9 207792-35-6,
3-Menthoxypropane-1,2-diol 211184-47-3 220621-22-7 381224-15-3
506412-91-5 521981-60-2 637336-79-9 697235-49-7 857557-19-8
1122460-01-8
RL: COS (Cosmetic use); THU (Therapeutic use); BIOL (Biological study);
USES (Uses)
(cosmeceutical compns. comprising polyalkylene glycols)

IT 170729-80-3
RL: COS (Cosmetic use); THU (Therapeutic use); BIOL (Biological study);
USES (Uses)
(cosmeceutical compns. comprising polyalkylene glycols)

RN 170729-80-3 CAPLUS
CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phen
yl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX
NAME)



Absolute stereochemistry shown
Rotation (+)

OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
BR 112017027546 A2	BR 2017-112017027546	Register
BR 112017027546 B1	BR 2017-112017027546	Register
CN 107847772 A	CN 2016-80045857	Register|Global Dossier
CN 107847772 B	CN 2016-80045857	Register|Global Dossier
EP 3108941 A1	EP 2015-173373	Register|Federated Reg.
EP 3108941 B1	EP 2015-173373	Register|Federated Reg.
IN 201717044256 A	IN 2017-17044256	Register
JP 2018518496 T	JP 2017-565942	Register|Global Dossier
JP 6945458 B2	JP 2017-565942	Register|Global Dossier
KR 2018015265 A	KR 2018-7002058	Register|Global Dossier
KR 2117171 B1	KR 2018-7002058	Register|Global Dossier
MX 2017016226 A	MX 2017-16226	Register
US 20180185301 A1	US 2017-15736494	Register|Global Dossier
WO 2016207084 A1	WO 2016-EP64109	Register|Global Dossier

L5 ANSWER 29 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2016:2116494 CAPLUS Full-text
DOCUMENT NUMBER: 172:545657
TITLE: Statistical investigation of simulated fed intestinal media composition on the equilibrium solubility of oral drugs
AUTHOR(S): Zhou, Zhou; Dunn, Claire; Khadra, Ibrahim; Wilson, Clive G.; Halbert, Gavin W.
CORPORATE SOURCE: Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow, G4 0RE, UK
SOURCE: European Journal of Pharmaceutical Sciences (2017), 99, 95-104
CODEN: EPSCED; ISSN: 0928-0987
DIGITAL OBJECT ID: 10.1016/j.ejps.2016.12.008
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
AB Gastrointestinal fluid is a complex milieu and it is recognized that gut drug soly. is different to that obsd. in simple aq. buffers. Simulated gastrointestinal media have been developed covering fasted and fed states to facilitate in vitro prediction of gut soly. and product dissoln. However, the combination of bile salts, phospholipids, fatty acids and proteins in an aq. buffered system creates multiple phases and drug soly. is therefore a complex interaction between these components, which may create unique environments for each API. The impact on soly. can be assessed through a statistical design of expt. (DoE) approach, to det. the influence and relationships between factors. In this paper DoE has been

applied to fed simulated gastrointestinal media consisting of eight components (pH, bile salt, lecithin, sodium oleate, monoglyceride, buffer, salt and pancreatin) using a two level D-optimal design with forty-four duplicate measurements and four center points. The equil. soly. of a range of poorly sol. acidic (indomethacin, ibuprofen, phenytoin, valsartan, zafirlukast), basic (aprepitant, carvedilol, tadalafil, bromocriptine) and neutral (fenofibrate, felodipine, probucol, itraconazole) drugs was investigated. Results indicate that the DoE provides equil. soly. values that are comparable to literature results for other simulated fed gastrointestinal media systems or human intestinal fluid samples. For acidic drugs the influence of pH predominates but other significant factors related to oleate and bile salt or interactions between them are present. For basic drugs pH, oleate and bile salt have equal significance along with interactions between pH and oleate and lecithin and oleate. Neutral drugs show diverse effects of the media components particularly with regard to oleate, bile salt, pH and lecithin but the presence of monoglyceride, pancreatin and buffer have significant but smaller effects on soly. There are fourteen significant interactions between factors mainly related to the surfactant components and pH, indicating that the soly. of neutral drugs in fed simulated media is complex. The results also indicate that the equil. soly. of each drug can exhibit individualistic behavior assocd. with the drug's chem. structure, physicochem. properties and interaction with media components. The utility of DoE for fed simulated media has been demonstrated providing equil. soly. values comparable with similar in vitro systems while also providing greater information on the influence of media factors and their interactions. The detn. of a drug's gastrointestinal soly. envelope provides useful limits that can potentially be applied to in silico modeling and in vivo expts.

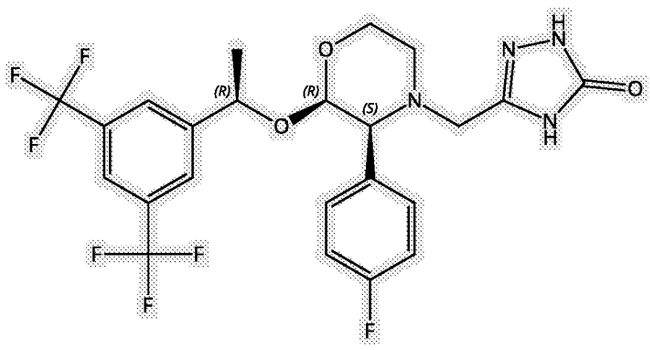
CC 63-5 (Pharmaceuticals)

IT 53-86-1, Indomethacin 57-41-0, Phenytoin 15687-27-1, Ibuprofen 23288-49-5, Probucol 25614-03-3, Bromocriptine 49562-28-9, Fenofibrate 72509-76-3, Felodipine 72956-09-3, Carvedilol 84625-61-6, Itraconazole 107753-78-6, Zafirlukast 137862-53-4, Valsartan 170729-80-3, Aprepitant 171596-29-5, Tadalafil
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(statistical investigation of simulated fed intestinal media compn. effect on equil. soly. of oral drugs)

IT 170729-80-3, Aprepitant
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(statistical investigation of simulated fed intestinal media compn. effect on equil. soly. of oral drugs)

RN 170729-80-3 CAPLUS

CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

OS.CITING REF COUNT: 34 THERE ARE 34 CAPLUS RECORDS THAT CITE THIS RECORD (34 CITINGS)

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 30 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2016:2039523 CAPLUS Full-text
DOCUMENT NUMBER: 167:295158
TITLE: Stable injectable pharmaceutical composition of neurokinin 1 receptor antagonist and process for preparation thereof
INVENTOR(S): Karavas, Evangelos; Koutris, Efthimios; Bikiaris, Dimitrios; Chatidou, Sotiria; Diakidou, Amalia; Barmpalexis, Panagiotis; Konstanti, Louiza; Minioti, Katerina
PATENT ASSIGNEE(S): Pharmathen S.A., Greece
ULTIMATE OWNER: PARTNERS GROUP HOLDING AG
ULTIMATE OWNER STANDARD: Partners Group
SOURCE: U.S. Pat. Appl. Publ., No pp. given
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20150165045	A1	20150618	US 2014-14412147	20141230
WO 2014005606	A1	20140109	WO 2012-EP2854	20120706
US 20200237920	A1	20200730	US 2020-16851779	20200417

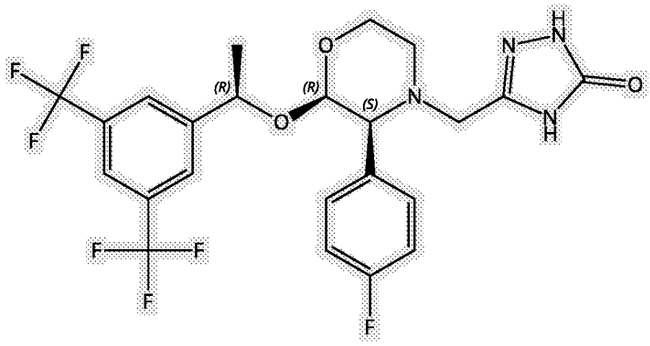
PRIORITY APPLN. INFO.: WO 2012-EP2854 W 20120706
US 2014-14412147 A1 20141230

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
US 20150165045	A1	Dead	20220105
WO 2014005606	A1	Dead	20201202
US 20200237920	A1	Dead	20231109

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASFORMULTNS 2016:2039523
AB The present invention relates to a controlled release sterile injectable formulation in the form of soln., suspension or sol-gel formulation for i.m. or s.c. administration comprising a therapeutically effective amt. of a neurokinin 1 receptor antagonist, in particular Aprepitant or Fosaprepitant or pharmaceutical acceptable salt, deriv. or metabolite thereof. It also relates to a process for developing such formulations.
IPCI A61K0047-38 [I]; A61K0031-675 [I]; A61K0047-34 [I]; A61K0047-44 [I]; A61K0047-14 [I]; A61K0047-46 [I]; A61K0031-5377 [I]; A61K0009-00 [I]
IPCR A61K0047-38 [I]; A61K0009-00 [I]; A61K0031-5377 [I]; A61K0031-675 [I]; A61K0047-14 [I]; A61K0047-34 [I]; A61K0047-44 [I]; A61K0047-46 [I]
NCL 514/090.000; 514/230.800
CC 63-6 (Pharmaceuticals)
IT Castor oil
Cottonseed oil
Gelatins
Lecithins
Polymers
Polyoxyalkylenes
Sesame oil
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. of stable injectable pharmaceutical compns. of neurokinin 1 receptor antagonist)
IT 170729-80-3 172673-20-0 265121-04-8
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. of stable injectable pharmaceutical compns. of neurokinin 1 receptor antagonist)
IT 170729-80-3
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. of stable injectable pharmaceutical compns. of neurokinin 1 receptor antagonist)
RN 170729-80-3 CAPLUS
CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX

NAME)



Absolute stereochemistry shown
Rotation (+)

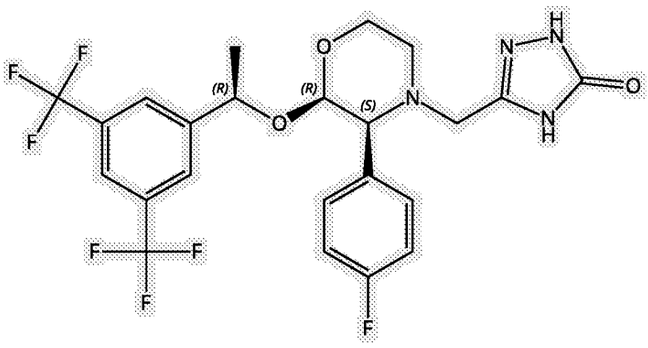
LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
US 20150165045 A1	US 2014-14412147	Register|Global Dossier
US 20200237920 A1	US 2020-16851779	Register|Global Dossier
WO 2014005606 A1	WO 2012-EP2854	Register|Global Dossier

L5 ANSWER 31 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2016:1859837 CAPLUS Full-text
DOCUMENT NUMBER: 166:232413
TITLE: Evaluation of Pentravan, Pentravan Plus, Phytobase, Lipovan and Pluronic Lecithin Organogel for the transdermal administration of antiemetic drugs to treat chemotherapy-induced nausea and vomiting at the hospital
AUTHOR(S): Bourdon, F.; Lecoeur, M.; Leconte, L.; Ultre, V.; Kouach, M.; Odou, P.; Vaccher, C.; Foulon, C.
CORPORATE SOURCE: EA GRITA-7365-Groupe de Recherche sur les formes Injectables et les Technologies Associees, Univ. Lille, Lille, F-59000, Fr.
SOURCE: International Journal of Pharmaceutics (Amsterdam, Netherlands) (2016), 515(1-2), 774-787
CODEN: IJPHDE; ISSN: 0378-5173
DIGITAL OBJECT ID: 10.1016/j.ijpharm.2016.11.014
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
OTHER SOURCE(S): CASFORMULTNS 2016:1859837

AB The objective of this study was to evaluate five com. ready-to-use transdermal vehicles (Phytobase, Lipovan, Pentravan, Pentravan Plus and Pluronic Lecithin Organogel (PLO)), for the compounding of three antiemetic drugs (ondansetron, dexamethasone and aprepitant) and their administration in combination to treat chemotherapy-induced nausea and vomiting (CINV) at the hospital. Drugs were individually formulated in these vehicles and in mixt. in Pentravan Plus using different penetration enhancers. Quality control of the forms has demonstrated that formulation process was mastered and convenient for the hospital (time required: 20 min). Diffusion expts. through synthetic membranes and pig ear epidermis performed using Franz-type diffusion cells, have shown that the release and permeation process were greater for ondansetron than for dexamethasone and aprepitant, with a release step not limiting. As permeation of aprepitant was too low, it was discarded of the study. When ondansetron and dexamethasone were compounded in combination in Pentravan Plus, the most efficient vehicle, a permeation decrease was obsd. Finally, the use of tween 20 instead of EtOH as chem. enhancer has led to 2-fold factor increase in the flux of dexamethasone, resulting in fluxes convenient for transdermal administration of ondansetron to a child, but insufficient for an adult and for dexamethasone.

CC 63-6 (Pharmaceuticals)
ST antiemitic Pentravan Plus Phytobase Lipovan Pluronic Lecithin Organogel skin
IT Antiemetics
Biological permeation
Chemotherapy
Child
Combination chemotherapy
Drug delivery systems
Drug toxicity
Homo sapiens
Human
Nausea
Organogels
Permeation enhancers
Skin
Solubility
Transdermal drug delivery systems
Vomiting
(evaluation of Pentravan, Pentravan Plus, Phytobase, Lipovan and Pluronic Lecithin Organogel for the transdermal administration of antiemetic drugs to treat chemotherapy-induced nausea and vomiting at the hospital)
IT 1610779-74-2, Pentravan 1610779-77-5, Pluronic Lecithin Organogel 2074721-57-4, Pentravan Plus 2074721-58-5, Phytobase 2074721-59-6, Lipovan
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(evaluation of Pentravan, Pentravan Plus, Phytobase, Lipovan and Pluronic Lecithin Organogel for the transdermal administration of antiemetic drugs to treat chemotherapy-induced nausea and vomiting at the hospital)
IT 50-02-2, Dexamethasone 99614-01-4, Ondansetron hydrochloride 170729-80-3, Aprepitant
RL: PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(evaluation of Pentravan, Pentravan Plus, Phytobase, Lipovan and Pluronic Lecithin Organogel for the transdermal administration of antiemetic drugs to treat chemotherapy-induced nausea and vomiting at the hospital)
IT 9005-64-5, Tween 20
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(evaluation of Pentravan, Pentravan Plus, Phytobase, Lipovan and Pluronic Lecithin Organogel for the transdermal administration of antiemetic drugs to treat chemotherapy-induced nausea and vomiting at the hospital)
IT 170729-80-3, Aprepitant
RL: PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(evaluation of Pentravan, Pentravan Plus, Phytobase, Lipovan and Pluronic Lecithin Organogel for the transdermal administration of antiemetic drugs to treat chemotherapy-induced nausea and vomiting at the hospital)
RN 170729-80-3 CAPLUS
CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)

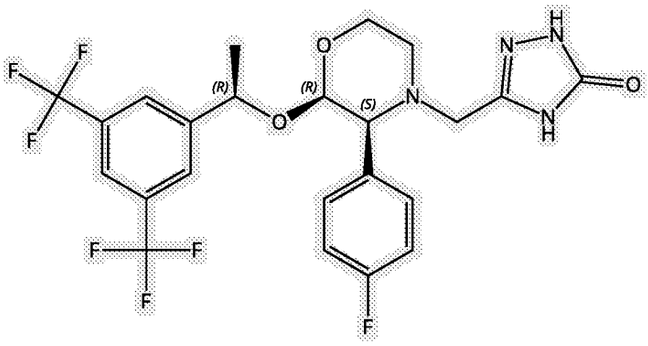


Absolute stereochemistry shown
Rotation (+)

OS.CITING REF COUNT: 14 THERE ARE 14 CAPLUS RECORDS THAT CITE THIS RECORD (15 CITINGS)
REFERENCE COUNT: 55 THERE ARE 55 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 32 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2016:1723954 CAPLUS Full-text
DOCUMENT NUMBER: 172:411315
TITLE: Optimization of the Ussing chamber setup with excised rat intestinal segments for dissolution/permeation experiments of poorly soluble drugs
AUTHOR(S): Forner, Kristin; Roos, Carl; Dahlgren, David; Kesisoglou, Filippos; Konerding, Moritz A.; Mazur, Johanna; Lennernaes, Hans; Langguth, Peter
CORPORATE SOURCE: Department of Pharmaceutical Technology and Biopharmaceutics, Johannes Gutenberg University, Mainz, Germany
SOURCE: Drug Development and Industrial Pharmacy (2017), 43(2), 338-346
CODEN: DDIPD8; ISSN: 0363-9045
DIGITAL OBJECT ID: 10.1080/03639045.2016.1251449
PUBLISHER: Taylor & Francis Ltd.
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
AB Prediction of the in vivo absorption of poorly sol. drugs may require simultaneous dissoln./permeation expts. In vivo predictive media have been modified for permeation expts. with Caco-2 cells, but not for excised rat intestinal segments. The present study aimed at improving the setup of dissoln./permeation expts. with excised rat intestinal segments by assessing suitable donor and receiver media. The regional compatibility of rat intestine in Ussing chambers with modified Fasted and Fed State Simulated Intestinal Fluids (Fa/FeSSIFmod) as donor media was evaluated via several parameters that reflect the viability of the excised intestinal segments. Receiver media that establish sink conditions were investigated for their foaming potential and toxicity. Dissoln./permeation expts. with the optimized conditions were then tested for two particle sizes of the BCS class II drug aprepitant. Fa/FeSSIFmod were toxic for excised rat ileal sheets but not duodenal sheets, the compatibility with jejunal segments depended on the bile salt concn. A non-foaming receiver medium contg. bovine serum albumin (BSA) and Antifoam B was nontoxic. With these conditions, the permeation of nanosized aprepitant was higher than of the unmilled drug formulations. The compatibility of Fa/FeSSIFmod depends on the excised intestinal region. The chosen conditions enable dissoln./permeation expts. with excised rat duodenal segments. The expts. correctly predicted the superior permeation of nanosized over unmilled aprepitant that is obsd. in vivo. The optimized setup uses FaSSIFmod as donor medium, excised rat duodenal sheets as permeation membrane and a receiver medium contg. BSA and Antifoam B.
CC 63-5 (Pharmaceuticals)
Section cross-reference(s): 9

IT Lecithins
RL: MOA (Modifier or additive use); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(optimization of Ussing chamber setup with excised rat intestinal segments for dissoln./permeation expts. of poorly sol. drugs)
IT 81-81-2, Warfarin 15307-86-5, Diclofenac 29122-68-7, Atenolol 170729-80-3, Aprepitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(optimization of Ussing chamber setup with excised rat intestinal segments for dissoln./permeation expts. of poorly sol. drugs)
IT 170729-80-3, Aprepitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(optimization of Ussing chamber setup with excised rat intestinal segments for dissoln./permeation expts. of poorly sol. drugs)
RN 170729-80-3 CAPLUS
CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

OS.CITING REF COUNT: 11 THERE ARE 11 CAPLUS RECORDS THAT CITE THIS RECORD (11 CITINGS)
REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 33 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2016:1057307 CAPLUS Full-text
DOCUMENT NUMBER: 165:169358
TITLE: Difficultly-soluble drug-containing nanostructure lipid carrier pharmaceutical composition with good solubility and high bioavailability and preparation method thereof
INVENTOR(S): Jin, Yinxiu; Wang, Yuxin; Tao, Xuefen; Shi, Lei; Shen, Peipei; Xia, Nianyou
PATENT ASSIGNEE(S): Taizhou Vocational & Technical College, Peop. Rep. China
SOURCE: Faming Zhuanli Shenqing, 21pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 105708799	A	20160629	CN 2016-10056874	20160127

PRIORITY APPLN. INFO.: CN 2016-10056874 20160127
PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
CN 105708799	A	Dead	20201120

OTHER SOURCE(S): CASFORMULTNS 2016:1057307
AB The title nanostructure lipid carrier pharmaceutical compn. is prepd. from

(by wt.%) difficultly-sol. drug (bezafibrate, oxcarbazepine, etc.) 0.02-1, solid lipid material (glyceryl monostearate, etc.) 0.3-15, liq. lipid material (soybean oil, etc.) 0.5-20, lipid-sol. emulsifier (lecithin and/or soybean phospholipid) 0.8-10, water-sol. emulsifier (Tween-20, etc.) 1-15 and water-sol. solvent (water, phosphate buffer soln., etc.) 39-97.38. The invention also provides a prepn. method of the nanostructure lipid carrier pharmaceutical compn. The inventive prepn. method has simple process, and good controllability and repeatability; and the inventive nanostructure lipid carrier pharmaceutical compn. contains difficultly-sol. drug, has good soly., degradability, physiol. compatibility and stability, and high bioavailability and entrapment rate, and no org. solvent residues, and can be used as drug delivery system for difficultly-sol. drug.

IPCI A61K0009-127; A61K0009-19; A61K0047-44; A61K0031-192; A61K0031-55; A61P0003-06; A61P0009-10

IPCR A61K0009-127 [I]; A61K0009-19 [I]; A61K0031-192 [I]; A61K0031-55 [I]; A61K0047-44 [I]; A61P0003-06 [I]; A61P0009-10 [I]

CC 63-6 (Pharmaceuticals)

IT Corn oil
Lecithins
Lipids
Peanut oil
Soya phospholipids
Soybean oil
Sunflower oil
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(difficultly-sol. drug-contg. nanostructure lipid carrier pharmaceutical compn. with good soly. and high bioavailability and prepn. method thereof)

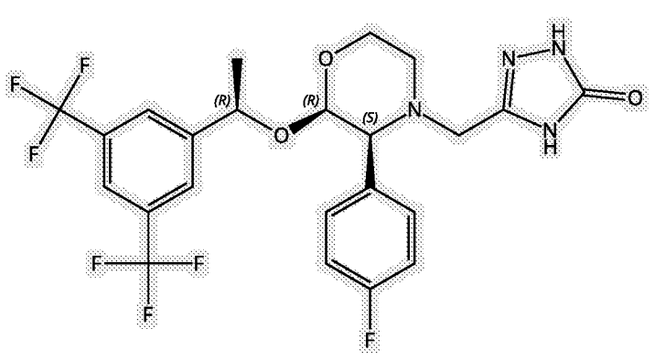
IT 50-14-6, Ergocalciferol 50-24-8, Prednisolone 50-28-2, Oestradiol, biological studies 51-48-9, L-Thyroxine, biological studies 52-01-7, Spironolactone 52-86-8, Haloperidol 53-43-0, Dehydroepiandrosterone 53-86-1, Indomethacin 55-98-1, Busulfan 57-83-0, Progesterone, biological studies 66-76-2, Bishydroxycoumarin 67-20-9, Furadantin 67-45-8, Furazolidone 67-96-9, Dihydrotachysterol 67-97-0, Cholecalciferol 68-26-8, Vitamin A 76-57-3, Codeine 76-99-3, Methadone 90-82-4, Pseudoephedrine 104-31-4, Benzonatate 113-15-5, Ergotamine 113-92-8 125-84-8, Aminoglutethimide 126-07-8, Griseofulvin 127-40-2, Xanthophyll 155-97-5, Pyridostigmine 298-46-4, 5H-Dibenz[b,f]azepine-5-carboxamide 298-57-7, Cinnarizine 298-81-7, Methoxsalen 300-62-9, Amfetamine 302-79-4, Tretinoin 303-49-1, Clomipramine 303-53-7, Cyclobenzaprine 303-98-0, Coenzyme Q10 303-98-0D, Ubidecarenone, salt deriv. 321-64-2, Tacrine 359-83-1, Pentazocine 378-44-9, Betamethasone 404-86-4, Capsaicin 437-38-7, Fentanyl 443-48-1, Metronidazole 502-65-8, Lycopene 511-12-6, Dihydroergotamine 520-85-4, Medroxyprogesterone 652-67-5, Isosorbitol 911-45-5, Clomifene 1134-47-0, Baclofen 1397-89-3, Amphotericin B 1406-16-2, Vitamin D 1406-18-4, Vitamin E 1665-48-1, Metaxalone 1951-25-3, Amiodarone 1972-08-3, Tetrahydrocannabinol 3562-63-8 4419-39-0, Beclomethasone 4759-48-2, Isotretinoin 5104-49-4, Flurbiprofen 7261-97-4, Dantrolene 7689-03-4, Camptothecin 10238-21-8, Glibenclamide 10238-21-8D, Glibenclamide, salt deriv. 10540-29-1, Tamoxifen 12001-79-5, Vitamin K 15307-86-5, Diclofenac 15574-96-6, Pizotifen 15686-51-8, Clemastine 17230-88-5, Danazol 17230-88-5D, Danazol, salt deriv. 18559-94-9, Salbutamol 19356-17-3, Calcifediol 20594-83-6, Nalbuphine 20830-75-5, Digoxin 21256-18-8, Oxaprozin 21829-25-4, Nifedipine 22916-47-8, Miconazole 23288-49-5, Probucol 25523-97-1, Dexchlorpheniramine 25812-30-0, Gemfibrozil 27203-92-5, Tramadol 28721-07-5, Oxcarbazepine 29094-61-9, Glipizide 29767-20-2, Teniposide 32222-06-3, Calcitriol 33069-62-4, Taxol 33419-42-0, Etoposide 34911-55-2, Bupropion 38304-91-5, Minoxidil 41340-25-4, Etodolac 41859-67-0, Bezafibrate 42924-53-8, Nabumetone 43200-80-2, Zopiclone 49562-28-9, Fenofibrate 49697-38-3, Rimexolone 51322-75-9, Tizanidine 51333-22-3, Budesonide 51481-61-9, Cimetidine 53123-88-9, Sirolimus 53179-11-6, Loperamide 53230-10-7, Mefloquine 54965-21-8, Albendazole 55079-83-9, Acitretin 55142-85-3, Ticlopidine 57469-82-6, Ibuprofen arginine 59467-70-8, Midazolam 59865-13-3, Cyclosporine 60142-96-3, Gabapentin 61379-65-5, Rifapentine 61869-08-7, Paroxetine 62013-04-1, Dirithromycin 63590-64-7, Terazosin 63612-50-0, Nilutamide 63675-72-9, Nisoldipine 65271-80-9, Mitoxantrone 65277-42-1, Ketoconazole 68506-86-5, Vigabatrin

69756-53-2, Halofantrine 70288-86-7, Ivermectin 72432-03-2, Miglitol
72559-06-9, Rifabutine 73590-58-6, Omeprazole 73963-72-1, Cilostazol
74103-06-3, Ketorolac 75330-75-5, Lovastatin 75706-12-6, Leflunomide
76547-98-3, Lisinopril 76824-35-6, Famotidine 76963-41-2, Nizatidine
79617-96-2, Sertraline 79794-75-5, Loratadine 79902-63-9, Simvastatin
80621-81-4, Rifaximin 81093-37-0, Pravastatin 81098-60-4, Cisapride
81103-11-9, Clarithromycin 82626-48-0, Zolpidem 83799-24-0,
Fexofenadine 83881-51-0, Cetirizine 83905-01-5, Azithromycin
84057-84-1, Lamotrigine 84371-65-3, Mifepristone 84449-90-1,
Raloxifene 84625-61-6, Itraconazole 85721-33-1, Ciprofloxacin
86386-73-4, Fluconazole 86541-75-5, Benazepril 88150-42-9, Amlodipine
89778-26-7, Toremifene 90357-06-5, Bicalutamide 91161-71-6,
Terbinafine 93390-81-9, Fosphenytoin 93413-69-5, Venlafaxine
93479-97-1, Glimepiride 93957-54-1, Fluvastatin 95233-18-4, Atovaquone
97240-79-4, Topiramate 97322-87-7, Troglitazone 97682-44-5, Irinotecan
98319-26-7, Finasteride 101828-21-1, Butenafine 103577-45-3,
Lansoprazole 103628-46-2, Sumatriptan 104987-11-3, Tacrolimus
106133-20-4, Tamsulosin 106650-56-0, Sibutramine 107753-78-6,
Zafirlukast 111025-46-8, Pioglitazone 111406-87-2, Zileuton
112965-21-6, Calcipotriene 113665-84-2, Clopidogrel 114977-28-5,
Docetaxel 115103-54-3, Tiagabine 117976-89-3, Rabeprazole
118292-40-3, Tazarotene 120014-06-4, Donepezil 121679-13-8,
Naratriptan 122320-73-4, Rosiglitazone 123948-87-8, Topotecan
127779-20-8, Saquinavir 129497-78-5, Verteporfin 131918-61-1,
Paricalcitol 133040-01-4, Eprosartan 134523-00-5, Atorvastatin
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Irbesartan 139264-17-8, Zolmitriptan 139481-59-7, Candesartan
139755-83-2, Sildenafil 144034-80-0, Rizatriptan 144494-65-5,
Tirofiban 144701-48-4, Telmisartan 145599-86-6, Cerivastatin
145941-26-0, Oprevelkin 146939-27-7, Ziprasidone 147059-72-1,
Trovafloxacin 153559-49-0, Targretin 154229-19-3, Abiraterone
154598-52-4, Efavirenz 155213-67-5, Ritonavir 158747-02-5,
Frovatriptan 158966-92-8, Montelukast 159989-64-7, Nelfinavir
162011-90-7, Rofecoxib 169590-42-5, Celecoxib 170729-80-3,
Aprepitant 290297-26-6, Netupitant 366789-02-8, Rivaroxaban
394730-60-0, Boceprevir 402957-28-2, Telaprevir
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)
(difficultly-sol. drug-contg. nanostructure lipid carrier
pharmaceutical compn. with good soly. and high bioavailability and
prepn. method thereof)

IT 170729-80-3, Aprepitant
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)
(difficultly-sol. drug-contg. nanostructure lipid carrier
pharmaceutical compn. with good soly. and high bioavailability and
prepn. method thereof)

RN 170729-80-3 CAPLUS

CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phen
yl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX
NAME)



Absolute stereochemistry shown
Rotation (+)

OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
CN 105708799 A	CN 2016-10056874	Register|Global Dossier

L5 ANSWER 34 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2016:725430 CAPLUS Full-text
DOCUMENT NUMBER: 164:573948
TITLE: Self-microemulsifying drug delivery system for improving bioavailability of poorly soluble drug and its application
INVENTOR(S): Li, Suhua; Li, Jixi
PATENT ASSIGNEE(S): Peop. Rep. China
SOURCE: Faming Zhuanli Shenqing, 23pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 105535979	A	20160504	CN 2015-10819197	20151122
CN 105535979	B	20190625		

PRIORITY APPLN. INFO.: CN 2015-10819197 20151122
PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
CN 105535979	A	Alive	20201121
CN 105535979	B	Alive	20201121

AB The present invention provides a novel self-microemulsifying drug delivery system (SEDDS), wherein the SEDDS carrier material comprises Capmul MCMs and medium-chain fatty acid-contg. oil phase and surfactant. It is suitable for loading two classes of poorly sol. drugs, including pH-dependent (weak acid, weak base drug) and non-pH-dependent (neutral drugs), greatly increases the soly. of the drug to achieve the optimal bioavailability, and has important application value in the formulation development of insol. drugs.
IPCI A61K0047-14 [I]; A61K0047-12 [I]; A61K0047-34 [I]; A61K0047-44 [I]; A61K0031-405 [I]; A61K0031-4515 [I]; A61K0031-58 [I]; A61K0047-14; A61K0047-12; A61K0047-10; A61K0047-44; A61K0031-405; A61K0031-4515; A61K0031-58
IPCR A61K0047-14 [I]; A61K0031-405 [I]; A61K0031-4515 [I]; A61K0031-58 [I]; A61K0047-12 [I]; A61K0047-34 [I]; A61K0047-44 [I]; A61K0047-14 [I]; A61K0047-10 [I]; A61K0047-44 [I]
CC 63-6 (Pharmaceuticals)
IT Acylcarnitines
Alcohols
Amino acids
Bile acids
Bile salts
Cephalins
Ceramides
Dipeptides
Ethoxylated hydrogenated castor oil
Gangliosides
Glycerides
Glycerophospholipids
Glycosphingolipids
Lecithins
Lysophosphatides
Lysophosphatidylcholines
Lysophosphatidylserines
Medium-chain fatty acids
Monoglycerides
Phosphatidic acids
Phosphatidylcholines
Phosphatidylserines
Phospholipids
Polyoxyalkylenes

Pyranosides
Sphingomyelins
Tripeptides
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(self-microemulsifying drug delivery system for improving bioavailability of poorly sol. drug and its application)

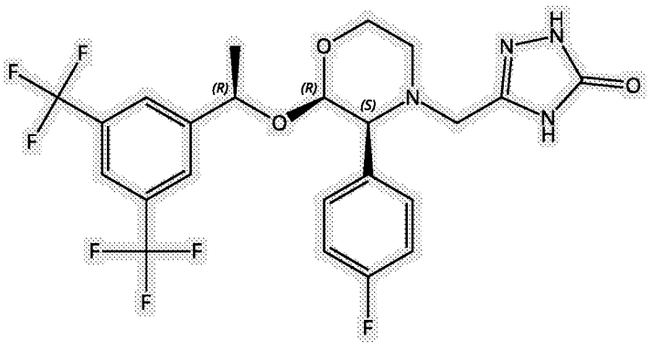
IT 50-14-6, Ergocalciferol 50-24-8, Prednisolone 50-28-2, Oestradiol, biological studies 51-48-9, L-Thyroxine, biological studies 52-01-7, Spironolactone 52-86-8, Haloperidol 53-43-0, Dehydroepiandrosterone 53-86-1, Indomethacin 55-98-1, Busulfan 57-83-0, Progestin, biological studies 66-76-2, Dicoumarol 67-20-9, Nitrofurantoin 67-45-8, Furazolidone 67-96-9, Dihydrotachysterol 67-97-0, Cholecal ciferol 68-26-8, Vitamin A 76-57-3, Codeine 76-99-3, Methadone 83-43-2, Methylprednisolone 90-82-4, Pseudoephedrine 104-31-4, Benzonatate 113-15-5, Ergotamine 113-92-8, Chlorphenamine maleate 125-84-8, Aminoglutethimide 126-07-8, Griseofulvin 127-40-2 155-97-5, Pyridostigmine 298-46-4, 5H-Dibenz[b,f]azepine-5-carboxamide 298-57-7, Cinnarizine 298-81-7, Methoxsalen 300-62-9, Amphetamine 302-79-4, Retinoic acid 303-49-1, Clomipramine 303-53-7, Cyclobenzaprine 303-98-0, Coenzyme Q10 321-64-2, Tacrine 359-83-1, Pentazocine 378-44-9, Betamethasone 404-86-4, Capsaicin 437-38-7, Fentanyl 443-48-1, Metronidazole 502-65-8, Lycopene 511-12-6, Dihydroergotamine 652-67-5, Isosorbitol 911-45-5, Clomifene 1134-47-0, Baclofen 1397-89-3, Amphotericin B 1406-16-2, Vitamin D 1406-18-4, Vitamin E 1665-48-1, Metaxalone 1951-25-3, Amiodarone 1972-08-3, Tetrahydrocannabinol 3562-63-8 4419-39-0, Beclomethasone 4759-48-2, Isotretinoin 5104-49-4, Flurbiprofen 7261-97-4, Dantrolene 7689-03-4, Camptothecin 10238-21-8, Glyburide 10540-29-1, Tamoxifen 12001-79-5, Vitamin K 15307-86-5, Diclofenac 15574-96-6, Pizotifen 15686-51-8, Clemastine 15687-27-1, Ibuprofen 17230-88-5, Danazol 18559-94-9, Salbutamol 19356-17-3, Calcifediol 20594-83-6, Nalbuphine 20830-75-5, Digoxin 21256-18-8, Oxaprozin 21829-25-4, Nifedipine 22916-47-8, Miconazole 23288-49-5, Probucol 25523-97-1, Dexchlorpheniramine 25812-30-0, Gemfibrozil 27203-92-5, Tramadol 29094-61-9, Glipizide 29767-20-2, Teniposide 32222-06-3, Calcitriol 33069-62-4, Paclitaxel 33419-42-0, Etoposide 34911-55-2, Bupropion 38304-91-5, Minoxidil 41340-25-4, Etodolac 42924-53-8, Nabumetone 43200-80-2, Zopiclone 49562-28-9, Fenofibrate 49697-38-3, Rimexolone 51322-75-9, Tizanidine 51333-22-3, Budesonide 51481-61-9, Cimetidine 53123-88-9, Sirolimus 53179-11-6, Loperamide 53230-10-7, Mefloquine 54965-21-8, Albendazole 55079-83-9, Acitretin 55142-85-3, Ticlopidine 59467-70-8, Midazolam 60142-96-3, Gabapentin 61379-65-5, Rifapentine 61869-08-7, Paroxetine 62013-04-1, Dirithromycin 63590-64-7, Terazosin 63612-50-0, Nilutamide 63675-72-9, Nisoldipine 65271-80-9, Mitoxantrone 65277-42-1, Ketoconazole 68506-86-5, Vigabatrin 69756-53-2, Halofantrine 70288-86-7, Ivermectin 72432-03-2, Miglitol 72559-06-9, Rifabutine 73590-58-6, Omeprazole 73963-72-1, Cilostazole 74103-06-3, Ketorolac 75330-75-5, Lovastatin 75706-12-6, Leflunomide 76547-98-3, Lisinopril 76824-35-6, Famotidine 76963-41-2, Nizatidine 79217-60-0, Cyclosporin 79617-96-2, Sertraline 79794-75-5, Loratadine 79902-63-9, Simvastatin 80621-81-4, Rifaximin 81093-37-0, Pravastatin 81098-60-4, Cisapride 81103-11-9, Clarithromycin 82626-48-0, Zolpidem 83799-24-0, Fexofenadine 83881-51-0, Cetirizine 83905-01-5, Azithromycin 84057-84-1, Lamotrigine 84371-65-3, Mifepristone 84449-90-1, Raloxifene 84625-61-6, Itraconazole 85721-33-1, Ciprofloxacin 86386-73-4, Fluconazole 86541-75-5, Benazepril 88150-42-9, Amlodipine 89778-26-7, Toremifene 90357-06-5, Bicalutamide 91161-71-6, Terbinafine 93390-81-9, Fosphenytoin 93413-69-5, Venlafaxine 93479-97-1, Glimepiride 93957-54-1, Fluvastatin 95233-18-4, Atovaquone 97240-79-4, Topiramate 97322-87-7, Troglitazone 97682-44-5, Irinotecan 98319-26-7, Finasteride 101828-21-1, Butenafine 103577-45-3, Lansoprazole 103628-46-2, Sumatriptan 104987-11-3, Tacrolimus 106133-20-4, Tamsulosin 106650-56-0, Sibutramine 107753-78-6, Zafirlukast 111025-46-8, Pioglitazone 111406-87-2, Zileuton 112965-21-6, Calcipotriene 113665-84-2, Clopidogrel 114977-28-5, Docetaxel 115103-54-3, Tiagabine 117976-89-3, Rabeprazole 118292-40-3, Tazarotene 120014-06-4, Donepezil 121679-13-8, Naratriptan 122320-73-4, Rosiglitazone 123948-87-8, Topotecan 127779-20-8, Saquinavir 129497-78-5, Verteporfin 131918-61-1, Paricalcitol 133040-01-4, Eprosartan 134523-00-5, Atorvastatin 135062-02-1, Repaglinide 137862-53-4, Valsartan 138402-11-6,

Irbesartan 139264-17-8, Zolmitriptan 139481-59-7, Candesartan 139755-83-2, Sildenafil 144034-80-0, Rizatriptan 144494-65-5, Tirofiban 144701-48-4, Telmisartan 145599-86-6, Cerivastatin 146939-27-7, Ziprasidone 147059-72-1, Trovafloxacin 153559-49-0, Targretin 154229-19-3, Abiraterone 154598-52-4, Efavirenz 155213-67-5, Ritonavir 158747-02-5, Frovatriptan 158966-92-8, Montelukast 159989-64-7, Nelfinavir 162011-90-7, Rofecoxib 169590-42-5, Celecoxib 170729-80-3, Aprepitant 290297-26-6, Netupitant 366789-02-8, Rivaroxaban 394730-60-0, Boceprevir 402957-28-2, Telaprevir
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(self-microemulsifying drug delivery system for improving bioavailability of poorly sol. drug and its application)

IT 170729-80-3, Aprepitant
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(self-microemulsifying drug delivery system for improving bioavailability of poorly sol. drug and its application)

RN 170729-80-3 CAPLUS

CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
CN 105535979 A	CN 2015-10819197	Register|Global Dossier
CN 105535979 B	CN 2015-10819197	Register|Global Dossier

L5 ANSWER 35 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN

ACCESSION NUMBER: 2016:535017 CAPLUS Full-text

DOCUMENT NUMBER: 164:512967

TITLE: Aprepitant loaded nanocrystal lipid microcapsule for treating nausea and vomiting after chemotherapy

INVENTOR(S): Zhu, Songlin; Xiao, Yan; Meng, Qingyue; Zhao, Yongxing; Cui, Hao; Chen, Yongqiang; Fang, Shuixia; Pan, Na; Chen, Shuiku; Liang, Qian; Luo, Feng; Liu, Jinxia; Yue, Xiaohui

PATENT ASSIGNEE(S): Furen Medicines Group Co., Ltd., Peop. Rep. China; Kaifeng Pharmaceutical (Group) Co., Ltd.; Henan Furen Pharmaceutical Technology Development Co., Ltd.

ULTIMATE OWNER: FUREN MEDICINE GROUP; KAIFENG PHARMACEUTICAL GROUP; HENAN FUREN MEDICAL TECH DEV

ULTIMATE OWNER STANDARD: FUREN MEDICINE GROUP; KAIFENG PHARMACEUTICAL GROUP; HENAN FUREN MEDICAL TECH DEV

SOURCE: Faming Zhuanli Shenqing, 7pp.
CODEN: CNXXEV

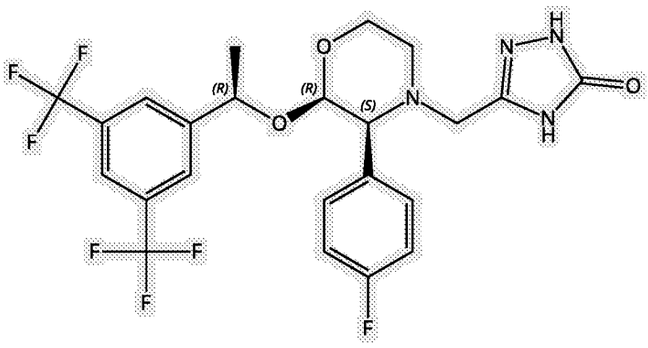
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 105456228	A	20160406	CN 2015-10928963	20151211
CN 105456228	B	20180605		

PRIORITY APPLN. INFO.: CN 2014-10814246 A 20141224
PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
CN 105456228	A	Alive	20201121
CN 105456228	B	Alive	20201121

OTHER SOURCE(S): CASFORMULTNS 2016:535017
AB The present invention provides an aprepitant loaded nanocrystal lipid microcapsule, and its prepn. method is as follows: prepg. aprepitant nanocrystals with av. particle size ranging from 50 nm to 400 nm with aprepitant and stabilizer through grinding, high-speed air-jet milling or high-pressure homogenization, dispersing in water and forming a suspension; after then, after dissolving phospholipid in an org. solvent, mixing and emulsifying with the aprepitant nanocrystals suspension, subsequently removing liq. phase, drying and obtaining prepd. the aprepitant nanocrystal lipid microcapsule; wherein the particle size distribution of aprepitant nanocrystal lipid microcapsules is 10-500 μm; the stabilizer is a mixt. of one or two and more of polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer, polyvinyl pyrrolidone, hydroxypropylmethyl cellulose, poloxamer and the like; the phospholipid is a mixt. of one or two and more of soybean phospholipid, lecithin and hydrogenated phospholipid. The above-mentioned aprepitant nanocrystal lipid microcapsule has stable properties, good in vivo absorption, high bioavailability and rapid drug efficacy functions; it can be used for treating nausea and vomiting after chemotherapy.
IPCI A61K0009-50; A61K0031-5377; A61K0047-24; A61P0001-08; A61P0025-24
IPCR A61K0009-50 [I]; A61K0031-5377 [I]; A61K0047-24 [I]; A61P0001-08 [I]; A61P0025-24 [I]
CC 63-6 (Pharmaceuticals)
IT Lecithins
Phospholipids
Soya phospholipids
RL: MOA (Modifier or additive use); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aprepitant loaded nanocrystal lipid microcapsule for treating nausea and vomiting after chemotherapy)
IT 170729-80-3, Aprepitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aprepitant loaded nanocrystal lipid microcapsule for treating nausea and vomiting after chemotherapy)
IT 170729-80-3, Aprepitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aprepitant loaded nanocrystal lipid microcapsule for treating nausea and vomiting after chemotherapy)
RN 170729-80-3 CAPLUS
CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
CN 105456228 A	CN 2015-10928963	Register|Global Dossier
CN 105456228 B	CN 2015-10928963	Register|Global Dossier

L5 ANSWER 36 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2016:473657 CAPLUS Full-text
DOCUMENT NUMBER: 164:387016
TITLE: Emulsion formulations of aprepitant
INVENTOR(S): Ottoboni, Thomas B.; Han, Han
PATENT ASSIGNEE(S): Heron Therapeutics, Inc., USA
ULTIMATE OWNER: HERON THERAPEUTICS, INC.
ULTIMATE OWNER STANDARD: HERON THERAPEUTICS, INC.
SOURCE: PCT Int. Appl., 36pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2016044784	A1	20160324	WO 2015-US51050	20150918
US 20160082013	A1	20160324	US 2015-14859013	20150918
US 9808465	B2	20171107		
KR 2017056575	A	20170523	KR 2017-7008598	20150918
KR 2424837	B1	20220725		
CN 106852118	A	20170613	CN 2015-80050449	20150918
EP 3193830	A1	20170726	EP 2015-772163	20150918
EP 3193830	B1	20231101		
EP 3193830	C0	20231101		
JP 2017533183	T	20171109	JP 2017-514863	20150918
JP 6741655	B2	20200819		
US 20160206622	A1	20160721	US 2016-15083071	20160328
US 9561229	B2	20170207		
US 20170112847	A1	20170427	US 2017-15398928	20170105
US 10500208	B2	20191210		
US 20180000828	A1	20180104	US 2017-15705201	20170914
US 9974793	B2	20180522		
US 20180000829	A1	20180104	US 2017-15705208	20170914
US 9974794	B2	20180522		
JP 2019196398	A	20191114	JP 2019-137539	20190726
US 20200197404	A1	20200625	US 2019-16669262	20191030
US 10953018	B2	20210323		
US 20210186981	A1	20210624	US 2021-17194114	20210305
JP 2022092040	A	20220621	JP 2022-66236	20220413
US 20240139201	A1	20240502	US 2024-18408463	20240109

PRIORITY APPLN. INFO.:

US 2014-62052948	P	20140919
JP 2017-514863	A3	20150918
US 2015-14859013	A1	20150918

WO 2015-US51050	W	20150918
US 2016-15083071	A1	20160328
US 2017-15398928	A1	20170105
JP 2019-137539	A3	20190726
US 2019-16669262	A1	20191030
US 2021-17194114	A1	20210305

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
WO 2016044784	A1	Dead	20201202
US 20160082013	A1	Alive	20201121
US 9808465	B2	Alive	20201120
KR 2017056575	A	Alive	20220602
KR 2424837	B1	Alive	20220811
CN 106852118	A	Transitional	20240307
EP 3193830	A1	Indeterminate	20240418
EP 3193830	B1	Indeterminate	20240418
EP 3193830	C0	Alive	20240104
JP 2017533183	T	Alive	20201121
JP 6741655	B2	Alive	20201121
US 20160206622	A1	Alive	20201120
US 9561229	B2	Alive	20201120
US 20170112847	A1	Alive	20201120
US 10500208	B2	Alive	20201120
US 20180000828	A1	Alive	20201121
US 9974793	B2	Alive	20201120
US 20180000829	A1	Alive	20201121
US 9974794	B2	Alive	20201120
JP 2019196398	A	Dead	20231026
US 20200197404	A1	Alive	20201121
US 10953018	B2	Alive	20210401
US 20210186981	A1	Transitional	20240321
JP 2022092040	A	Dead	20231207
US 20240139201	A1	Alive	20240509

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OTHER SOURCE(S): CASFORMULTNS 2016:473657

AB Disclosed herein are novel pharmaceutical formulations of aprepitant suitable for parenteral administration including i.v. administration. Also included are formulations including both aprepitant and dexamethasone sodium phosphate. The pharmaceutical formulations are stable oil-in-water emulsions for non-oral treatment of emesis and are particularly useful for treatment of subjects undergoing cancer chemotherapy.

IPCI A61K0009-00 [I]; A61K0047-10 [I]; A61K0047-44 [I]; A61K0047-24 [I]; A61K0047-12 [I]; A61K0047-26 [I]

IPCR A61K0009-00 [I]; A61K0047-10 [I]; A61K0047-12 [I]; A61K0047-24 [I]; A61K0047-26 [I]; A61K0047-44 [I]

CC 63-6 (Pharmaceuticals)

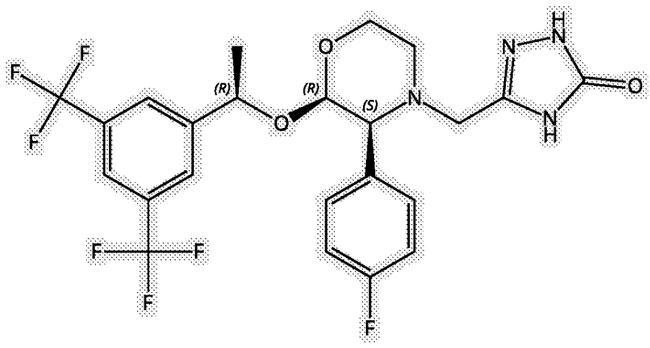
IT Alcohols
Egg yolk lecithins
Phospholipids
Soybean oil
RL: COS (Cosmetic use); BIOL (Biological study); USES (Uses)
(emulsion formulations of aprepitant)

IT 2392-39-4 170729-80-3
RL: PKT (Pharmacokinetics); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(emulsion formulations of aprepitant)

IT 170729-80-3
RL: PKT (Pharmacokinetics); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(emulsion formulations of aprepitant)

RN 170729-80-3 CAPLUS

CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
CN 106852118 A	CN 2015-80050449	Register|Global Dossier
EP 3193830 A1	EP 2015-772163	Register|Federated Reg.
EP 3193830 B1	EP 2015-772163	Register|Federated Reg.
EP 3193830 C0	EP 2015-772163	Register|Federated Reg.
JP 2017533183 T	JP 2017-514863	Register|Global Dossier
JP 6741655 B2	JP 2017-514863	Register|Global Dossier
JP 2019196398 A	JP 2019-137539	Register|Global Dossier
JP 2022092040 A	JP 2022-66236	Register|Global Dossier
KR 2017056575 A	KR 2017-7008598	Register|Global Dossier
KR 2424837 B1	KR 2017-7008598	Register|Global Dossier
US 20160082013 A1	US 2015-14859013	Register|Global Dossier
US 9808465 B2	US 2015-14859013	Register|Global Dossier
US 20160206622 A1	US 2016-15083071	Register|Global Dossier
US 9561229 B2	US 2016-15083071	Register|Global Dossier
US 10500208 B2	US 2017-15398928	Register|Global Dossier
US 20170112847 A1	US 2017-15398928	Register|Global Dossier
US 20180000828 A1	US 2017-15705201	Register|Global Dossier
US 9974793 B2	US 2017-15705201	Register|Global Dossier
US 20180000829 A1	US 2017-15705208	Register|Global Dossier
US 9974794 B2	US 2017-15705208	Register|Global Dossier
US 10953018 B2	US 2019-16669262	Register|Global Dossier
US 20200197404 A1	US 2019-16669262	Register|Global Dossier
US 20210186981 A1	US 2021-17194114	Register|Global Dossier
US 20240139201 A1	US 2024-18408463	Register|Global Dossier
WO 2016044784 A1	WO 2015-US51050	Register|Global Dossier

L5 ANSWER 37 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2015:1470836 CAPLUS Full-text
DOCUMENT NUMBER: 163:403366
TITLE: Method for manufacture of nano suspension
INVENTOR(S): Wang, Yongjun; Han, Xiangfei; Xue, Peng; Wang, Jing; Jiang, Mengjuan; He, Zhonggui
PATENT ASSIGNEE(S): Shenyang Pharmaceutical University, Peop. Rep. China
SOURCE: Faming Zhuanli Shenqing, 14pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 104887626	A	20150909	CN 2015-10287997	20150529

PRIORITY APPLN. INFO.: CN 2015-10287997 20150529

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
CN 104887626	A	Dead	20201120

AB The present invention relates to a method for manuf. of nano suspension, belonging to the field of pharmaceutical prepns. The present invention utilizes an effervescent method to generate bubbles for dispersion and mixing to obtain nano-suspensions, and includes the following specific steps : mixing drug, stabilizer, the org. acid and other pharmaceutically acceptable excipients as org. phase, dissolving carbonate and other pharmaceutically acceptable excipients in water as carbonate phase, mixing the two phases, or shaking or vortex, to obtain nano suspension. The drug contg. prescription comprises drugs 1, stabilizer 0. 01-20, org. acids 0. 01 -10, carbonate 0. 01 -10 wt. parts. The carbonate is sodium carbonate, potassium carbonate, KHCO3, CaCO3, calcium bicarbonate, ammonium carbonate, etc. The org. acid is malic acid, citric acid, succinic acid, sorbic acid, formic acid, acetic acid, propionic acid. The stabilizer is PEG 1000 vitamin E succinate, Tween, Span, poloxamer, etc. The drug is insol. anticancer drug, insol. antifungal drug, insol. antimicrobial agent, hypotensive drug, etc. The present invention significantly improves the soly. and dissoln. rate of poorly sol. drugs, thereby increases the bioavailability of poorly sol. drugs.

IPCI A61K0009-10 [I]; A61K0047-12 [I]; A61K0047-04 [I]; A61K0045-00 [I]

IPCR A61K0009-10 [I]; A61K0045-00 [I]; A61K0047-04 [I]; A61K0047-12 [I]

CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1

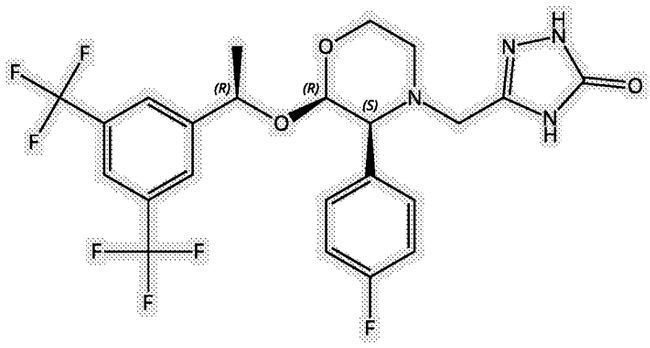
IT Amino acids
Carbonates
Ethoxylated hydrogenated castor oil
Fatty acids
Fatty alcohols
Gelatins
Lecithins
Organic acids
Phospholipids
Polyoxyalkylenes
Taxanes
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(method for manuf. of pharmaceutical nano suspension)

IT 50-02-2, Dexamethasone 52-01-7, Spirolactone 443-48-1, Metronidazole 595-33-5, Megestrol acetate 1397-89-3, Amphotericin B 7689-03-4, Camptothecin 9002-96-4, TPGS 10238-21-8, Glibenclamide 15307-86-5, Diclofenac 15687-27-1, Ibuprofen 16773-42-5, Ornidazole 23593-75-1, Clotrimazole 29767-20-2, Teniposide 33069-62-4, Taxol 33419-42-0, Etoposide 39562-70-4, Nitrendipine 53123-88-9, Sirolimus 55985-32-5, Nicardipine 66085-59-4, Nimodipine 79794-75-5, Loratadine 84625-61-6, Itraconazole 93479-97-1, Glimepiride 103577-45-3, Lansoprazole 104987-11-3, Tacrolimus 170729-80-3, Aprepitant 183133-96-2, Cabazitaxel 199739-10-1, Paliperidone palmitate
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(method for manuf. of pharmaceutical nano suspension)

IT 170729-80-3, Aprepitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(method for manuf. of pharmaceutical nano suspension)

RN 170729-80-3 CAPLUS

CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
CN 104887626 A	CN 2015-10287997	Register|Global Dossier

L5 ANSWER 38 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2015:1390403 CAPLUS Full-text
DOCUMENT NUMBER: 163:369597
TITLE: Compositions of pentosan polysulfate salts for oral administration and methods of use
INVENTOR(S): Parsons, C. Lowell; Goldberg, Michael; Meenan, Christopher P.
PATENT ASSIGNEE(S): Urigen Pharmaceuticals, Inc., USA
ULTIMATE OWNER: PLATINUM MONTAUR LIFE SCIENCES
ULTIMATE OWNER STANDARD: PLATINUM MONTAUR LIFE SCIENCES
SOURCE: PCT Int. Appl., 248pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2015127416	A1	20150827	WO 2015-US17205		20150224
CA 2949480	A1	20150827	CA 2015-2949480		20150224
AU 2015218642	A1	20161006	AU 2015-218642		20150224
EP 3110427	A1	20170104	EP 2015-751441		20150224
KR 2017003527	A	20170109	KR 2016-7026610		20150224
CN 106456662	A	20170222	CN 2015-80022057		20150224
JP 2017512757	T	20170525	JP 2016-554267		20150224
US 20170189443	A1	20170706	US 2016-15121312		20160824
PRIORITY APPLN. INFO.:			US 2014-61943824	P	20140224
			WO 2015-US17205	W	20150224

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
WO 2015127416	A1	Dead	20201201
CA 2949480	A1	Dead	20220428
AU 2015218642	A1	Dead	20210318
EP 3110427	A1	Dead	20210729
KR 2017003527	A	Alive	20201121
CN 106456662	A	Dead	20201121
JP 2017512757	T	Alive	20201120
US 20170189443	A1	Dead	20210324

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): MARPAT 163:369597; CASFORMULTNS 2015:1390403
AB The invention is directed to a pharmaceutical compn. comprising: (1) a therapeutically effective quantity of sodium pentosan polysulfate; (2) a quantity of a penetration enhancer sufficient to improve the bioavailability of the sodium pentosan polysulfate; and (3) optionally, a

pharmaceutically acceptable carrier and to methods for the oral administration of sodium pentosan polysulfate with improved bioavailability for the treatment of interstitial cystitis and other urinary tract diseases and conditions. Such compns. and methods allow the administration of sodium pentosan polysulfate at lower dosages to reduce the frequency and severity of side effects.

IPCI A61K0031-715 [I]; C07H0005-10 [I]; A61K0047-14 [I]; A61P0019-02 [I]

IPCR A61K0031-715 [I]; A61K0047-14 [I]; A61P0019-02 [I]; C07H0005-10 [I]

CC 1-12 (Pharmacology)

IT Acrylic polymers
Acylcarnitines
Amino acids
Bile salts
Bone morphogenetic protein 7
Bone sialoproteins
Cartilage oligomeric matrix protein
Collagen type I
Collagen type II
Collagen type IX
Collagen type XI
Collagens
Crown compounds
Dendrimers
Diglycerides
Estrogens
Fatty acids
Insulin-like growth factor-binding protein 3
Lecithins
Matrix proteins
Medium-chain fatty acids
Monoclonal antibodies
Monoglycerides
Opioids
Osteocalcins
Osteonectin
Osteopontin
Peptides
Polyanhydrides
Polyoxyalkylenes
Proteins
Salicylates
Steroidal hormones
Sulfonanilides
Terpenes
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. of pentosan polysulfate salts for oral administration and methods of use)

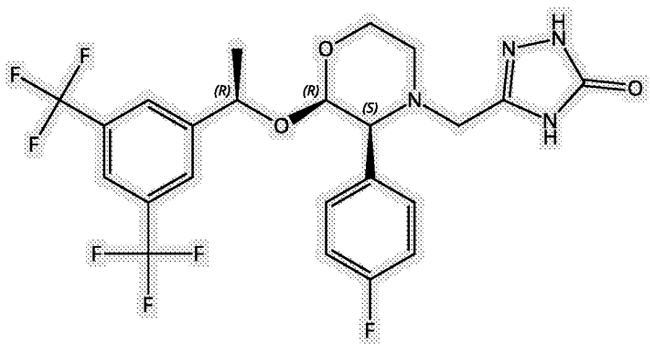
IT 15866-90-7, Metastat 15880-03-2 16011-96-4, 2-Iminopiperidine hydrochloride 16067-69-9, Strontium benzenesulfonate 16088-89-4, Strontium maleate 16139-18-7, Aminoguanidine hydrochloride 18847-18-2 19767-45-4, Mesna 19878-22-9 19982-08-2, Memantine 20093-91-8 20594-83-6, Nalbuphine 21084-57-1, 8-(Phthalimido)caprylic acid 21256-18-8, Oxaprozin 21463-31-0, 2-Amino-5,6-dihydro-6-methyl-4H-1,3-thiazine hydrochloride 22059-21-8, 1-Aminocyclopropane-1-carboxylic acid 22071-15-4, Ketoprofen 22204-53-1, Naproxen 22410-94-2 22494-42-4, Diflunisal 22834-47-5 24314-23-6 24339-95-5 25087-26-7 25087-26-7D, derivs. 25322-68-3 25496-72-4 25518-54-1 25587-34-2 26009-03-0, Poly[oxy(1-oxo-1,2-ethanediyl)] 26023-30-3, Poly[oxy(1-methyl-2-oxo-1,2-ethanediyl)] 26100-51-6, Polylactic acid 26124-68-5, Polyglycolic acid 26171-23-3, Tolmetin 26615-21-4, Zotepine 26864-56-2, Penfluridol 27203-92-5, Tramadol 27261-86-5 27540-07-4 27638-00-2 28945-89-3, 3-(3-Ethoxyphenyl)propanoic acid 28945-91-7, 3-(3-Butoxyphenyl)propanoic acid 29679-58-1, Fenoprofen 30762-02-8, 4-(Cyclopentyloxy)benzoic acid 31477-60-8, Ormeloxifene 33369-31-2, Zomepirac 34346-01-5 34816-55-2, Moxestrol 35197-20-7 36322-90-4, Piroxicam 36330-86-6 36440-58-1 36978-49-1 38194-50-2, Sulindac 39860-99-6, Pipotiazine 40182-75-0, Strontium citrate 40391-99-9 40472-00-2, Strontium succinate 41340-25-4, Etodolac 41839-80-9 42408-82-2, Butorphanol 42907-92-6 42907-93-7 43218-50-4 47739-98-0, Clocapramine 49594-75-4 50700-72-6,

Vecuronium 51036-98-7 51333-22-3, Budesonide 51803-78-2, Nimesulide
52240-14-9 52349-26-5 52485-79-7, Buprenorphine 52888-70-7,
3-(3-Phenoxyphenyl)propanoic acid 53583-79-2, Sultopride 53597-27-6,
Fendosal 53648-55-8, Dezocine 53716-49-7, Carprofen 53772-83-1,
Zuclopenthixol 57648-21-2, Timiperone 57821-78-0 59122-46-2,
Misoprostol 59227-89-3 59804-37-4, Tenoxicam 59865-13-3,
Cyclosporine 60118-07-2, Endorphin 61126-74-7 61126-76-9
63471-88-5 64228-79-1, Atracurium 64779-07-3 64779-14-2
65576-45-6, Asenapine 66644-81-3, Veralipride 67763-96-6, Insulin like
growth factor-1 68047-06-3, 4-Hydroxy-tamoxifen 68134-81-6,
Gacyclidine 71125-38-7, Meloxicam 71675-85-9, Amisulpride
74103-06-3, Ketorolac 75221-40-8, [4-(Cyclohexylmethoxy)phenyl]acetic
acid 75221-43-1 75272-39-8, Nemonapride 75706-12-6, Leflunomide
77086-21-6, Dizocilpine 77599-17-8, Panomifene 78994-23-7,
Levormeloxifene 79055-68-8 79669-11-7, 3-(4-Isopropoxyphenyl)propanoic
acid 79778-41-9, Neridronate 80125-14-0, Remoxipride 81093-37-0,
Pravastatin 81109-85-5 82413-20-5, Droloxifene 83015-26-3,
Atomoxetine 84449-90-1, Raloxifene 86111-26-4, Zindoxifene
89326-69-2, 5-(4-Ethylphenyl)pentanoic acid 89419-40-9, Mosapramine
89750-15-2, Glucagon like peptide-2 89778-26-7, Toremifene 89987-06-4,
Tiludronate 93957-54-1, Fluvastatin 98007-99-9 98774-23-3,
Tesmilifene 100759-29-3 100944-08-9 101253-68-3 102676-47-1,
Fadrozole 103735-76-8, erythro-MEA 103987-16-2 105462-24-6,
Risedronate 106266-06-2, Risperidone 106516-24-9, Sertindole
107868-30-4, Exemestane 108179-99-3 110347-85-8, Selfotel
110931-77-6 111974-69-7, Quetiapine 112809-51-5, Letrozole
114084-78-5, Ibandronate 115767-74-3, TAT-59 116057-68-2
116057-75-1, Idoxifene 117910-70-0 117928-94-6, Rapastinel
118072-93-8, Zoledronic acid 119431-25-3, Eliprodil 120511-73-1,
Anastrozole 121368-58-9, Olpadronate 122004-99-3 123663-49-0, T-614
124937-51-5, Tolterodine 124937-52-6, Detrol 128298-28-2, Remacemide
128607-22-7, Ospemifene 129318-43-0 129453-61-8, Fulvestrant
129612-87-9, Miproxifene 129722-12-9, Aripiprazole 129731-10-8,
Vorozole 129948-69-2 130370-59-1, GI-129471 130370-60-4, Batimastat
131123-76-7, 5,7-Dichlorokynurenic acid 131692-21-2 132539-06-1,
Olanzapine 132810-10-7, Blonanserin 133454-47-4, Iloperidone
133814-18-3, Doxacurium 134523-00-5, Atorvastatin 135459-87-9,
Strontium ranelate 136013-76-8, 2-(Cyclopropylmethoxy)benzoic acid
136553-81-6, BQ-123 136982-36-0, CP-99994 137159-92-3, Aptiganel
137945-48-3, CT-3 138330-18-4, Incadronate 141620-66-8 142880-36-2,
Ilomastat 144598-75-4, Paliperidone 145599-86-6, Cerivastatin
146490-38-2 146939-27-7, Ziprasidone 147536-97-8, Bosentan
148215-77-4, 2-(Cyclopentyloxy)benzoic acid 148700-85-0, L-733060
150403-89-7 150915-41-6, Perospirone 153322-05-5, Lanicemine
153438-49-4, RPR-100893 154039-60-8, Marimastat 155383-07-6, SDZ-PTS
893 156161-89-6, BQ-788 156806-79-0 157116-68-2 157116-71-7
158089-95-3, S-2474 158860-95-8, 3-(Cyclohexylmethoxy)benzoic acid
158860-99-2, 3-(Cyclopentyloxy)benzoic acid 159190-44-0 162011-90-7,
Rofecoxib 162752-13-8, 3-(4-Propylphenyl)propanoic acid 165536-41-4,
MDL-103323 168158-16-5, KB-R-7785 168266-90-8, Vofopitant
168980-06-1 168980-07-2 168980-08-3 168980-09-4 168980-10-7
168980-12-9 168980-13-0 169590-41-4, Deracoxib 169590-42-5,
Celecoxib 169799-04-6, MMI-270 169799-44-4, Keratin sulfate
170277-31-3, Infliximab 170566-84-4, Lanepitant 170713-75-4
170729-80-3, Aprepitant 172673-20-0, Fosaprepitant
173937-91-2, Atrasentan 175033-36-0, NCX4016 177036-94-1, Ambrisentan
177172-49-5 177653-18-8 177653-31-5 177653-36-0 177653-53-1
177653-62-2 177653-65-5 179545-77-8, Tanomastat 180064-38-4
180384-57-0, Tezosentan
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)
(compns. of pentosan polysulfate salts for oral administration and
methods of use)

IT 170729-80-3, Aprepitant
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)
(compns. of pentosan polysulfate salts for oral administration and
methods of use)

RN 170729-80-3 CAPLUS

CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phen
yl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX
NAME)



Absolute stereochemistry shown
Rotation (+)

OS.CITING REF COUNT: 5 THERE ARE 5 CAPLUS RECORDS THAT CITE THIS RECORD (5 CITINGS)
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
AU 2015218642 A1	AU 2015-218642	Register
CA 2949480 A1	CA 2015-2949480	Register
CN 106456662 A	CN 2015-80022057	Register|Global Dossier
EP 3110427 A1	EP 2015-751441	Register|Federated Reg.
JP 2017512757 T	JP 2016-554267	Register|Global Dossier
KR 2017003527 A	KR 2016-7026610	Register|Global Dossier
US 20170189443 A1	US 2016-15121312	Register|Global Dossier
WO 2015127416 A1	WO 2015-US17205	Register|Global Dossier

L5 ANSWER 39 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2015:865407 CAPLUS Full-text
DOCUMENT NUMBER: 162:663467
TITLE: Orally disintegrating porous film comprising pharmacological active ingredient and method for preparing the same
INVENTOR(S): Oh, Dong Hoon; Lee, Jin Hoo; Lee, So Yi; Kang, Jun Hyuk; Lim, Chae Yun; Jung, Kyung Tae; Yeon, Kyu Jeong; Park, Jin Gyu
PATENT ASSIGNEE(S): Seoul Pharma. Co., Ltd., S. Korea
ULTIMATE OWNER: SEOUL PHARMA. CO., LTD.
ULTIMATE OWNER STANDARD: SEOUL PHARMA. CO., LTD.
SOURCE: PCT Int. Appl., 30pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Korean
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

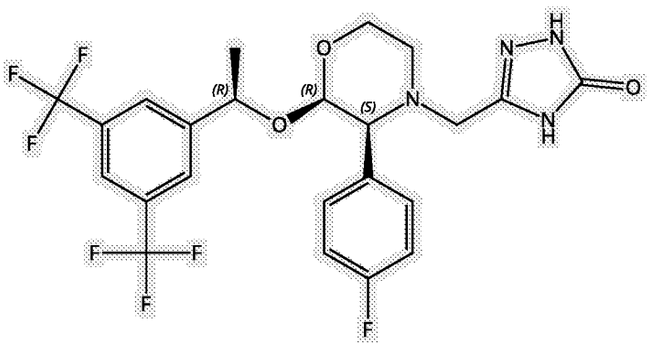
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2015072684	A1	20150521	WO 2014-KR10293	20141030
KR 1407922	B1	20140617	KR 2013-138040	20131114
CN 105873572	A	20160817	CN 2014-80071821	20141030
EP 3069716	A1	20160921	EP 2014-861454	20141030
US 20160279071	A1	20160929	US 2016-15036784	20160513
PRIORITY APPLN. INFO.:			KR 2013-138040 A	20131114
			WO 2014-KR10293 W	20141030

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
WO 2015072684	A1	Dead	20201202
KR 1407922	B1	Dead	20201121
CN 105873572	A	Dead	20201121

EP 3069716 A1 Dead 20201203
US 20160279071 A1 Dead 20201121
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASFORMULTNS 2015:865407
AB The present invention relates to an orally disintegrating porous film and a method for prepg. the same, the film comprising a foaming agent, a foam stabilizing agent, a plasticizer, and pharmacol. active ingredient. The orally disintegrating porous film according to the present invention has micropores within the film and phys. properties suitable for a film, so that the film has an effect of significantly improving the dissoln. rate of a drug and has good processability since the film can be easily prepd. at low cost and through a simplified prepn. method.
IPCI A61K0009-70 [I]; A61P0003-10 [I]; A61P0003-04 [I]
IPCR A61K0009-70 [I]; A61P0003-04 [I]; A61P0003-10 [I]
CC 63-6 (Pharmaceuticals)
IT Alditols
Enzymes
Hormones, animal
Lecithins
Medium-chain fatty acids
Polyoxyalkylenes
Vitamins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(orally disintegrating porous film comprising pharmacol. active substance and its manufg. method)
IT 50-02-2, Dexamethasone 50-58-8, Phendimetrazine tartrate 50-81-7, L-Ascorbic acid, biological studies 54-11-5, Nicotine 55-63-0, Nitroglycerin 56-81-5, Glycerin, biological studies 56-81-5D, Glycerin, fatty acid esters 57-50-1D, Sucrose, fatty acid esters 57-55-6, Propylene glycol, biological studies 58-08-2, Caffeine, biological studies 61-76-7, Phenylephrine hydrochloride 90-84-6, Diethylpropion 94-09-7, Benzocaine 102-76-1, Triacetin 103-90-2, Acetaminophen 113-92-8 123-03-5, Cetylpyridinium chloride 124-90-3, Oxycodone hydrochloride 125-69-9, Dextromethorphan bromide 147-24-0, Diphenhydramine hydrochloride 345-78-8, Pseudoephedrine hydrochloride 357-08-4, Naloxone hydrochloride 437-38-7, Fentanyl 562-10-7 569-65-3, Meclizine 797-63-7, Levonorgestrel 1134-47-0, Baclofen 1197-21-3, Phentermine hydrochloride 1508-65-2, Oxybutynin hydrochloride 2216-51-5, L-Menthol 7232-21-5, Metoclopramide hydrochloride 7384-98-7, Propylene glycol dicaprylate 8050-81-5, Simethicone 9000-30-0, Guar gum 9000-40-2, Locust bean gum 9000-69-5, Pectin 9003-20-7, Polyvinyl acetate 9004-65-3, Hydroxypropyl methyl cellulose 9005-25-8, Starch, biological studies 9005-25-8D, Starch, derivs. 9005-32-7, Alginic acid 9057-02-7, Pullulan 11138-66-2, Xanthan gum 12441-09-7D, Sorbitan, fatty acid esters 14611-52-0, Selegiline hydrochloride 15307-86-5, Diclofenac 15687-27-1, Ibuprofen 16679-58-6, Desmopressin 22071-15-4, Ketoprofen 22232-71-9, Mazindol 23828-92-4, Ambroxol hydrochloride 25322-68-3, Polyethylene oxide 27848-84-6, Nicergoline 28911-01-5, Triazolam 28981-97-7, Alprazolam 31565-12-5, Propylene glycol monocaprylate 34552-83-5, Loperamide hydrochloride 37220-82-9, Glycerol oleate 41100-52-1, Memantine hydrochloride 51481-61-9, Cimetidine 52485-79-7, Buprenorphine 56211-40-6, Torasemide 59729-32-7, Citalopram hydrobromide 64461-82-1, Tizanidine hydrochloride 66357-59-3, Ranitidine hydrochloride 71125-38-7, Meloxicam 72797-41-2, Tianeptine 73590-58-6, Omeprazole 76824-35-6, Famotidine 77883-43-3, Doxazosin mesylate 79794-75-5, Loratadine 82248-59-7, Atomoxetine hydrochloride 82626-48-0, Zolpidem 83480-29-9, Voglibose 83881-52-1, Cetirizine hydrochloride 84057-84-1, Lamotrigine 87333-19-5, Ramipril 90729-43-4, Ebastine 93479-97-1, Glimepiride 97240-79-4, Topiramate 99614-01-4, Ondansetron hydrochloride 99614-02-5, Ondansetron 100299-08-9, Pemirolast potassium 100643-71-8, Desloratadine 103577-45-3, Lansoprazole 103628-46-2, Sumatriptan 106133-20-4, Tamsulosin 106266-06-2, Risperidone 109889-09-0, Granisetron 112885-41-3, Mosapride 119356-77-3, Dapoxetine 120011-70-3, Donepezil hydrochloride 129722-12-9, Aripiprazole 132539-06-1, Olanzapine 132907-72-3, Ramosetron hydrochloride 139264-17-8, Zolmitriptan 139755-83-2, Sildenafil 140462-76-6, Olopatadine hydrochloride 144034-80-0, Rizatriptan 144689-63-4, Olmesartan medoxomil 151767-02-1, Montelukast sodium 153439-40-8, Fexofenadine hydrochloride 158966-92-8, Montelukast 170729-80-3, Aprepitant 171596-29-5, Tadalafil 171599-83-0, Sildenafil citrate 219861-08-2, Escitalopram oxalate

224785-91-5, Vardenafil hydrochloride 242478-38-2, Solifenacin succinate
246852-12-0, Amlodipine mesylate 268203-93-6, Udenafil 286930-03-8,
Fesoterodine fumarate 385367-47-5, Tarafenacin 823178-28-5
862189-96-6
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(orally disintegrating porous film comprising pharmacol. active
substance and its manufg. method)
IT 170729-80-3, Aprepitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(orally disintegrating porous film comprising pharmacol. active
substance and its manufg. method)
RN 170729-80-3 CAPLUS
CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phen
yl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX
NAME)



Absolute stereochemistry shown
Rotation (+)

OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD
(1 CITINGS)
REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
CN 105873572 A	CN 2014-80071821	Register|Global Dossier
EP 3069716 A1	EP 2014-861454	Register|Federated Reg.
KR 1407922 B1	KR 2013-138040	Register|Global Dossier
US 20160279071 A1	US 2016-15036784	Register|Global Dossier
WO 2015072684 A1	WO 2014-KR10293	Register|Global Dossier

L5 ANSWER 40 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2014:2053394 CAPLUS Full-text
DOCUMENT NUMBER: 162:85982
TITLE: Lipid, protein, and/or cationic molecule coated pharmaceutically active particles and compositions comprising same
INVENTOR(S): Chawrai, Suresh; Prasad, Sudhanand; Bajaj, Kirti
PATENT ASSIGNEE(S): Vyome Biosciences Pvt. Ltd., India
ULTIMATE OWNER: VYOME THERAPEUTICS LIMITED
ULTIMATE OWNER STANDARD: Vyome
SOURCE: PCT Int. Appl., 221pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2014195872	A1	20141211	WO 2014-IB61925	20140603
CA 2914583	A1	20141211	CA 2014-2914583	20140603
CA 2914583	C	20190618		

AU 2014276460	A1	20151224	AU 2014-276460		20140603
IL 242916	A	20160131	IL 2014-242916		20140603
KR 2016015335	A	20160212	KR 2015-7037272		20140603
KR 1814895	B1	20180104			
CN 105407718	A	20160316	CN 2014-80042031		20140603
CN 105407718	B	20190104			
EP 3003031	A1	20160413	EP 2014-739231		20140603
JP 2016523232	T	20160808	JP 2016-517716		20140603
BR 112015030501	A2	20170725	BR 2015-112015030501		20140603
NZ 714817	A	20170728	NZ 2014-714817		20140603
US 20160128944	A1	20160512	US 2015-14895738		20151203
MX 2015016675	A	20160715	MX 2015-16675		20151203
IN 2015CN07967	A	20160831	IN 2015-CN7967		20151224
AU 2017203374	A1	20170608	AU 2017-203374		20170519
AU 2018282407	A1	20190117	AU 2018-282407		20181221
PRIORITY APPLN. INFO.:			IN 2013-DE1684	A	20130604
			AU 2014-276460	A3	20140603
			WO 2014-IB61925	W	20140603
			AU 2017-203374	A3	20170519

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
WO 2014195872	A1	Dead	20201201
CA 2914583	A1	Dead	20221013
CA 2914583	C	Dead	20221013
AU 2014276460	A1	Dead	20201121
KR 2016015335	A	Alive	20201121
KR 1814895	B1	Alive	20201121
CN 105407718	A	Dead	20221117
CN 105407718	B	Dead	20221117
EP 3003031	A1	Dead	20210715
JP 2016523232	T	Alive	20201121
BR 112015030501	A2	Alive	20210729
NZ 714817	A	Dead	20210820
US 20160128944	A1	Dead	20210408
MX 2015016675	A	Alive	20201120
AU 2017203374	A1	Alive	20201121
AU 2018282407	A1	Dead	20210708

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OTHER SOURCE(S): CASFORMULTNS 2014:2053394

AB The invention provides species of lipid, protein, and/or cationic mol. coated active agents and compns. comprising the coated particles. The compns. can be personal care compns. such as anti-dandruff shampoo or conditioner, skin care compns., creams, gels, toothpastes, mouth washes, and chewing gums.

IPCI A01N0025-12 [I]; A01N0025-34 [I]; A01N0037-06 [I]; A01N0043-12 [I]; A01N0043-40 [I]; A01N0057-12 [I]; A01N0059-16 [I]; A61K0008-11 [I]; A61K0008-49 [I]; A61Q0005-00 [I]; A61K0031-44 [I]; A61Q0019-00 [I]; A61K0009-00 [I]; A61K0031-496 [I]

IPCR A01N0025-34 [I]; A01N0025-12 [I]; A01N0037-06 [I]; A01N0043-12 [I]; A01N0043-40 [I]; A01N0057-12 [I]; A01N0059-16 [I]; A61K0008-11 [I]; A61K0008-49 [I]; A61K0009-00 [I]; A61K0031-44 [I]; A61K0031-496 [I]; A61Q0005-00 [I]; A61Q0019-00 [I]

CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 62

IT Actins
Albumins
Alkaloids
Aminoglycosides
Androgens
Antibodies and Immunoglobulins
Apricot kernel oil
Avocado oil
Blood proteins
Carbapenems
Carbohydrates
Caseins
Citronella oil
Coal tar
Coconut oil
Collagen hydrolyzates
Collagens

Conchiolins
Corticosteroids
Curcuminoids
Echinocandins
Egg yolk lecithins
Elastins
Estrogens
Ethoxylated hydrogenated castor oil
Fibroin
Fibronectins
Flavanoids
Flavonoids
Fructooligosaccharides
Galactooligosaccharides
Gelatin hydrolyzates
Glycerolipids
Glycerophospholipids
Glycopeptides
Glycosaminoglycans
Hemoglobins
Hydrocarbon oils
Immunoglobulin fragments
Indoles
Integrins
Keratins
Ketolides
Lactalbumins
Lipids
Macrolides
Milk proteins
Neem oil
Oligosaccharides
Oxazolidinones
Palmarosa oil
Paraffin oils
Peppermint oil
Peptide analogs
Peptides
Phosphatidic acids
Phosphatidylcholines
Phosphatidylethanolamines
Phosphatidylinositol 4,5-bisphosphate
Phosphatidylinositol 4-phosphate
Phosphatidylinositols
Phosphatidylinositols
Phosphatidylserines
Phospholipids
Podophyllum (resin)
Polyamines
Polyamines (nonpolymeric)
Polyketides
Polyoxyalkylenes
Polysaccharides
Progestogens
Pyrethroids
Reticulin
Retinoids
Sericin hydrolyzates
Sericins
Soya lecithins
Soybean proteins
Sphingolipids
Sterols
Sulfonamides
Sunflower oil
Sweet orange peel oil
Tetracyclines
Tocopherols
Zeins
β-Lactams
RL: COS (Cosmetic use); THU (Therapeutic use); BIOL (Biological study);
USES (Uses)

(lipid and protein and/or cationic mol. coated pharmaceutically active particles and compns. comprising same)

IT 84625-61-6, Itraconazole 84957-29-9, Cefpirome 85233-19-8, 1,2-Bis(o-aminophenoxy)ethane-N,N,N',N'-tetraacetic acid 85441-61-8, Quinapril 85622-93-1, Temozolomide 85650-52-8, Mirtazapine 85721-33-1, Ciprofloxacin 86003-55-6, Nikkomycin 86386-73-4, Fluconazole 86541-75-5, Benazepril 86697-97-4, Sensomer CT-250 87061-04-9 87239-81-4, Cefpodoxime proxetil 87848-99-5, Acrivastine 88040-23-7, Cefepime 88150-42-9, Amlodipine 89365-50-4, Salmeterol 91161-71-6, Terbinafine 91374-21-9, Ropinirole 91832-40-5, Cefdinir 92348-62-4, Hydroxycaprylic acid 92665-29-7, Cefprozil 93413-69-5, Venlafaxine 95058-81-4, Gemcitabine 96036-03-2, Meropenem 97321-87-4 97519-39-6, Ceftibuten 97682-44-5, Irinotecan 98079-51-7, Lomefloxacin 99011-02-6, Imiquimod 99592-32-2, Sertaconazole 99614-02-5, Ondansetron 100643-71-8, Desloratadine 100986-85-4, Levofloxacin 101828-21-1, Butenafine 103060-53-3, Daptomycin 103577-45-3, Lansoprazole 103775-14-0, Moexiprilat 104227-87-4, Famciclovir 104632-26-0, Pramipexole 105462-24-6, Risedronic acid 105956-97-6, Clinafloxacin 106133-20-4, Tamsulosin 106266-06-2, Risperidone 106392-12-5, Poloxamer 407 106516-24-9, Sertindole 106650-56-0, Sibutramine 106685-40-9, Adapalene 107233-08-9, Cevimeline 107753-78-6, Zafirlukast 108319-06-8, Temafloxacin 110871-86-8, Sparfloxacin 111025-46-8, Pioglitazone 111974-69-7, Quetiapine 112362-50-2, Dalfopristin 112809-51-5, Letrozole 112811-59-3, Gatifloxacin 112965-21-6, Calcipotriene 113170-55-1 113665-84-2, Clopidogrel 113775-47-6, Dexmedetomidine 113806-05-6, Olopatadine 114798-26-4, Losartan 115103-54-3, Tiagabine 115256-11-6, Dofetilide 115956-12-2, Dolasetron 116539-59-4, Duloxetine 117467-28-4, Cefditoren pivoxil 117976-89-3, Rabeprazole 118292-40-3, Tazarotene 119141-88-7, Esomeprazole 119914-60-2, Grepafloxacin 120014-06-4, Donepezil 120138-50-3, Quinupristin 120279-96-1, Dorzolamide 120511-73-1, Anastrozole 121028-76-0 121708-81-4 123441-03-2, Rivastigmine 124937-51-5, Tolterodine 127045-41-4, Pazufloxacin 127254-12-0, Sitafloxacin 128196-01-0, Escitalopram 129618-40-2, Nevirapine 129639-79-8 129722-12-9, Aripiprazole 132539-06-1, Olanzapine 132781-92-1 134678-17-4, Lamivudine 135729-61-2, Palonosetron 136470-78-5, Abacavir 136817-59-9, Delavirdine 137234-62-9, Voriconazole 138402-11-6, Irbesartan 139264-17-8, Zolmitriptan 139755-83-2, Sildenafil 141388-76-3, Besifloxacin 142340-99-6, Adefovir dipivoxil 143322-58-1, Eletriptan 143491-57-0, Emtricitabine 144034-80-0, Rizatriptan 144377-73-1, Linoleamidopropyl PG-dimonium chloride phosphate 144494-65-5, Tirofiban 144689-63-4, Olmesartan medoxomil 144701-48-4, Telmisartan 145040-37-5, Candesartan cilexetil 145158-71-0, Tegaserod 146939-27-7, Ziprasidone 147059-72-1, Trovafloxacin 150378-17-9, Indinavir 151096-09-2, Moxifloxacin 151319-34-5, Zaleplon 151581-81-6, Pradimicin 152459-95-5, Imatinib 154323-57-6, Almotriptan 154592-20-8, Copper pyrithione 156259-68-6, Capmul MCM 159989-64-7, Nelfinavir 161465-32-3, Elaidolinolenyl alcohol 162011-90-7, Rofecoxib 162808-62-0, Caspofungin 165800-03-3, Linezolid 166663-25-8, Anidulafungin 169590-42-5, Celecoxib 170729-80-3, Aprepitant 171228-49-2, POsaconazole 171596-29-5, Tadalafil 175357-18-3 175463-14-6, Gemifloxacin 177933-73-2D, AMP (acrylate polymer), allyl methacrylate copolymer 179463-17-3, Cancidas 182760-06-1, Ravuconazole 184475-35-2, Gefitinib 187949-02-6, Albaconazole 188627-80-7, Eptifibatide 191114-48-4, Telithromycin 194804-75-6 195868-36-1, Phenyl trimethicone 198904-31-3, Atazanavir 201341-05-1, Tenofovir disoproxil 201531-68-2D, Pyridazinone, dimorpholino deriv. 220222-14-0, Lithium pyrithione 220222-18-4, Strontium pyrithione 224785-90-4, Vardenafil 226256-56-0, Cinacalcet 235114-32-6, Micafungin 241479-67-4, Isavuconazole 313998-09-3, Gold pyrithione 351420-48-9 351420-50-3 374629-79-5 433711-29-6, Carbopol Aqua SF 1 463965-85-7, Behentrimonium methosulfate 506412-91-5 577746-42-0 608514-56-3 830331-83-4 881038-57-9, Zinc selenide sulfide 915764-71-5 951216-62-9 1477911-63-9, Dimethicone PEG-7 Isostearate 1639929-04-6

RL: COS (Cosmetic use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(lipid and protein and/or cationic mol. coated pharmaceutically active particles and compns. comprising same)

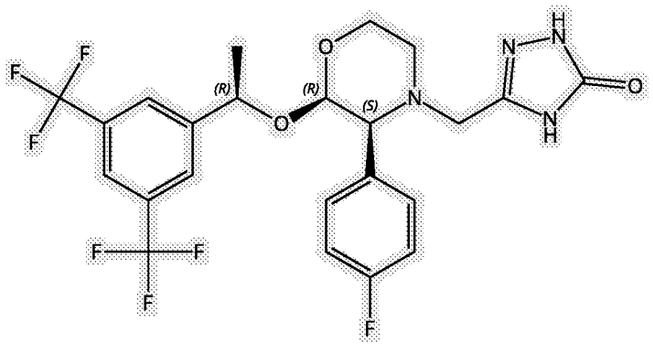
IT 170729-80-3, Aprepitant

RL: COS (Cosmetic use); THU (Therapeutic use); BIOL (Biological study);

USES (Uses)
(lipid and protein and/or cationic mol. coated pharmaceutically active particles and compns. comprising same)

RN 170729-80-3 CAPLUS

CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

OS.CITING REF COUNT: 17 THERE ARE 17 CAPLUS RECORDS THAT CITE THIS RECORD (18 CITINGS)

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
AU 2014276460 A1	AU 2014-276460	Register
AU 2017203374 A1	AU 2017-203374	Register
AU 2018282407 A1	AU 2018-282407	Register
BR 112015030501 A2	BR 2015-112015030501	Register
CA 2914583 A1	CA 2014-2914583	Register
CA 2914583 C	CA 2014-2914583	Register
CN 105407718 A	CN 2014-80042031	Register|Global Dossier
CN 105407718 B	CN 2014-80042031	Register|Global Dossier
EP 3003031 A1	EP 2014-739231	Register|Federated Reg.
IL 242916 A	IL 2014-242916	Register
IN 2015CN07967 A	IN 2015-CN7967	Register
JP 2016523232 T	JP 2016-517716	Register|Global Dossier
KR 1814895 B1	KR 2015-7037272	Register|Global Dossier
KR 2016015335 A	KR 2015-7037272	Register|Global Dossier
MX 2015016675 A	MX 2015-16675	Register
NZ 714817 A	NZ 2014-714817	Register
US 20160128944 A1	US 2015-14895738	Register|Global Dossier
WO 2014195872 A1	WO 2014-IB61925	Register|Global Dossier

L5 ANSWER 41 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN

ACCESSION NUMBER: 2014:1944702 CAPLUS Full-text

DOCUMENT NUMBER: 164:453599

TITLE: Statistical investigation of simulated intestinal fluid composition on the equilibrium solubility of biopharmaceutics classification system class II drugs

AUTHOR(S): Khadra, Ibrahim; Zhou, Zhou; Dunn, Claire; Wilson, Clive G.; Halbert, Gavin

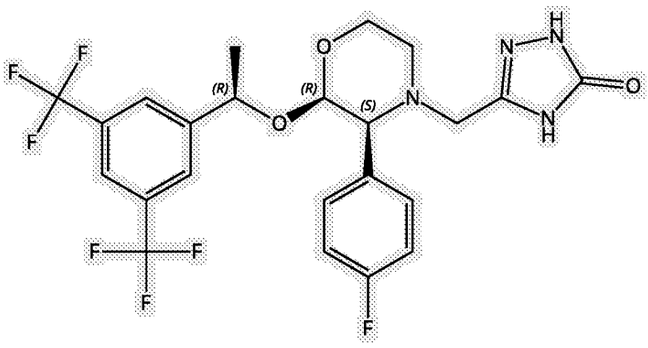
CORPORATE SOURCE: Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow, G4 0RE, UK

SOURCE: European Journal of Pharmaceutical Sciences (2015), 67, 65-75
CODEN: EPSCED; ISSN: 0928-0987

DIGITAL OBJECT ID: 10.1016/j.ejps.2014.10.019

PUBLISHER: Elsevier B.V.

DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
AB A drug's soly. and dissoln. behavior within the gastrointestinal tract is a key property for successful administration by the oral route and one of the key factors in the biopharmaceutics classification system. This property can be detd. by investigating drug soly. in human intestinal fluid (HIF) but this is difficult to obtain and highly variable, which has led to the development of multiple simulated intestinal fluid (SIF) recipes. Using a statistical design of expt. (DoE) technique this paper has investigated the effects and interactions on equil. drug soly. of seven typical SIF components (sodium taurocholate, lecithin, sodium phosphate, sodium chloride, pH, pancreatin and sodium oleate) within concn. ranges relevant to human intestinal fluid values. A range of poorly sol. drugs with acidic (naproxen, indomethacin, phenytoin, and piroxicam), basic (aprepitant, carvedilol, zafirlukast, tadalafil) or neutral (fenofibrate, griseofulvin, felodipine and probucol) properties have been investigated. The equil. soly. results detd. are comparable with literature studies of the drugs in either HIF or SIF indicating that the DoE is operating in the correct space. With the exception of pancreatin, all of the factors individually had a statistically significant influence on equil. soly. with variations in magnitude of effect between the acidic and basic or neutral compds. and drug specific interactions were evident. Interestingly for the neutral compds. pH was the factor with the second largest soly. effect. Around one third of all the possible factor combinations showed a significant influence on equil. soly. with variations in interaction significance and magnitude of effect between the acidic and basic or neutral compds. The least no. of significant media component interactions were noted for the acidic compds. with three and the greatest for the neutral compds. at seven, with again drug specific effects evident. This indicates that a drug's equil. soly. in SIF is influenced depending upon drug type by between eight to fourteen individual or combinations of media components with some of these drug specific. This illustrates the complex nature of these fluids and provides for individual drugs a visualisation of the possible soly. envelope within the gastrointestinal tract, which may be of importance for modeling in vivo behavior. In addn. the results indicate that the design of expt. approach can be employed to provide greater detail of drug soly. behavior, possible drug specific interactions and influence of variations in gastrointestinal media components due to disease. The approach is also feasible and amenable to adaptation for high throughput screening of drug candidates.
CC 63-5 (Pharmaceuticals)
IT 53-86-1, Indomethacin 57-41-0, Phenytoin 126-07-8, Griseofulvin 22204-53-1, Naproxen 23288-49-5, Probucol 36322-90-4, Piroxicam 49562-28-9, Fenofibrate 72509-76-3, Felodipine 72956-09-3, Carvedilol 107753-78-6, Zafirlukast 170729-80-3, Aprepitant 171596-29-5, Tadalafil
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(statistical investigation of simulated intestinal fluid compn. on equil. soly. of biopharmaceutics classification system class II drugs)
IT 170729-80-3, Aprepitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(statistical investigation of simulated intestinal fluid compn. on equil. soly. of biopharmaceutics classification system class II drugs)
RN 170729-80-3 CAPLUS
CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

OS.CITING REF COUNT: 55 THERE ARE 55 CAPLUS RECORDS THAT CITE THIS RECORD (55 CITINGS)
REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 42 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2014:1014062 CAPLUS Full-text
DOCUMENT NUMBER: 161:132468
TITLE: Orally disintegrating film comprising pharmacologically active substance and its manufacturing method
INVENTOR(S): Oh, Dong Hun; Lee, Jin Hu; Lee, So I.; Kang, Jun Hyeok; Lim, Chae Yun; Jung, Gyeong Tae; Yeon, Gyu Jeong; Park, Jin Gyu
PATENT ASSIGNEE(S): Seoul Pharmaceutical Co., Ltd., S. Korea
ULTIMATE OWNER: SEOUL PHARMA. CO., LTD.
ULTIMATE OWNER STANDARD: SEOUL PHARMA. CO., LTD.
SOURCE: Repub. Korea, 15pp.
CODEN: KRXXFC
DOCUMENT TYPE: Patent
LANGUAGE: Korean
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
KR 1407922	B1	20140617	KR 2013-138040		20131114
WO 2015072684	A1	20150521	WO 2014-KR10293		20141030
CN 105873572	A	20160817	CN 2014-80071821		20141030
EP 3069716	A1	20160921	EP 2014-861454		20141030
US 20160279071	A1	20160929	US 2016-15036784		20160513
PRIORITY APPLN. INFO.:			KR 2013-138040	A	20131114
			WO 2014-KR10293	W	20141030

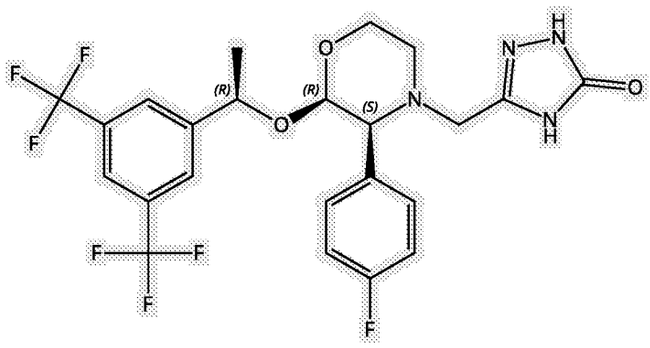
PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
KR 1407922	B1	Dead	20201121
WO 2015072684	A1	Dead	20201202
CN 105873572	A	Dead	20201121
EP 3069716	A1	Dead	20201203
US 20160279071	A1	Dead	20201121

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASFORMULTNS 2014:1014062
AB The title film has porosity of 10-35%, and contains more than one bubbling agent selected from nonionic surfactant, cationic surfactant, anionic surfactant and zwitterionic surfactant, more than one bubble stabilizer selected from pullulan, hydroxypropyl Me cellulose, polyvinyl acetate, polyethylene oxide, xanthan gum, guar gum, locust bean gum, starch, starch deriv., pectin, pectin hydrolyzate, alginic acid and alginic acid hydrolyzate, more than one plasticizer selected from glycerin, glycerol oleate, medium chain fatty acid, polyethylene glycol, propylene glycol, propylene glycol monocaprylate, propylene glycol dicaprylate, sugar, sugar

alc. and triacetin, and pharmacol. active substance.
IPCI A61K0009-70 [I]; A61P0003-10 [I]; A61P0003-04 [I]
IPCR A61K0009-70 [I]; A61P0003-04 [I]; A61P0003-10 [I]
CC 63-6 (Pharmaceuticals)
IT Alditols
Enzymes
Hormones, animal
Lecithins
Medium-chain fatty acids
Polyoxyalkylenes
Vitamins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(orally disintegrating porous film comprising pharmacol. active substance and its manufg. method)
IT 50-02-2, Dexamethasone 50-58-8, Phendimetrazine tartrate 50-81-7, L-Ascorbic acid, biological studies 54-11-5, Nicotine 55-63-0, Nitroglycerin 56-81-5, Glycerin, biological studies 56-81-5D, Glycerin, fatty acid esters 57-50-1, Sugar, biological studies 57-50-1D, Sucrose, fatty acid esters 57-55-6, Propylene glycol, biological studies 58-08-2, Caffeine, biological studies 61-76-7, Phenylephrine hydrochloride 90-84-6, Diethylpropion 94-09-7, Benzocaine 102-76-1, Triacetin 103-90-2, Acetaminophen 113-92-8 123-03-5, Cetylpyridinium chloride 124-90-3, Oxycodone hydrochloride 125-69-9, Dextromethorphan bromide 147-24-0, Diphenhydramine hydrochloride 345-78-8, Pseudoephedrine hydrochloride 357-08-4, Naloxone hydrochloride 437-38-7, Fentanyl 562-10-7 569-65-3, Meclizine 797-63-7, Levonorgestrel 1134-47-0, Baclofen 1197-21-3, Phentermine hydrochloride 1508-65-2, Oxybutynin hydrochloride 2216-51-5, L-Menthol 7232-21-5, Metoclopramide hydrochloride 7384-98-7, Propylene glycol dicaprylate 8050-81-5, Simethicone 9000-30-0, Guar gum 9000-40-2, Locust bean gum 9000-69-5, Pectin 9003-20-7, Polyvinyl acetate 9004-65-3, Hydroxypropyl methyl cellulose 9005-25-8, Starch, biological studies 9005-25-8D, Starch, derivs. 9005-32-7, Alginic acid 9057-02-7, Pullulan 11138-66-2, Xanthan gum 12441-09-7D, Sorbitan, fatty acid esters 14611-52-0, Selegiline hydrochloride 15307-86-5, Diclofenac 15687-27-1, Ibuprofen 16679-58-6, Desmopressin 22071-15-4, Ketoprofen 22232-71-9, Mazindol 23828-92-4, Ambroxol hydrochloride 25322-68-3, Polyethylene oxide 27848-84-6, Nicergoline 28911-01-5, Triazolam 28981-97-7, Alprazolam 31565-12-5, Propylene glycol monocaprylate 34552-83-5, Loperamide hydrochloride 37220-82-9, Glycerol oleate 41100-52-1, Memantine hydrochloride 51481-61-9, Cimetidine 52485-79-7, Buprenorphine 56211-40-6, Torasemide 59729-32-7, Citalopram hydrobromide 64461-82-1, Tizanidine hydrochloride 66357-59-3, Ranitidine hydrochloride 71125-38-7, Meloxicam 72797-41-2, Tianeptine 73590-58-6, Omeprazole 76824-35-6, Famotidine 77883-43-3, Doxazosin mesylate 79794-75-5, Loratadine 82248-59-7, Atomoxetine hydrochloride 83480-29-9, Voglibose 83881-52-1, Cetirizine hydrochloride 84057-84-1, Lamotrigine 87333-19-5, Ramipril 90729-43-4, Ebastine 93479-97-1, Glimepiride 97240-79-4, Topiramate 99614-01-4, Ondansetron hydrochloride 99614-02-5, Ondansetron 100299-08-9, Pemirolast potassium 100643-71-8, Desloratadine 103577-45-3, Lansoprazole 103628-46-2, Sumatriptan 106133-20-4, Tamsulosin 106266-06-2, Risperidone 109889-09-0, Granisetron 112885-41-3, Mosapride 119356-77-3, Dapoxetine 120011-70-3, Donepezil hydrochloride 129722-12-9, Aripiprazole 132539-06-1, Olanzapine 132907-72-3, Ramosetron hydrochloride 139264-17-8, Zolmitriptan 139755-83-2, Sildenafil 140462-76-6, Olopatadine hydrochloride 144034-80-0, Rizatriptan 144689-63-4, Olmesartan medoxomil 151767-02-1, Montelukast sodium 153439-40-8, Fexofenadine hydrochloride 158966-92-8, Montelukast 170729-80-3, Aprepitant 171596-29-5, Tadalafil 171599-83-0, Sildenafil citrate 219861-08-2, Escitalopram oxalate 224785-91-5, Vardenafil hydrochloride 242478-38-2, Solifenacin succinate 246852-12-0, Amlodipine mesylate 268203-93-6, Udenafil 286930-03-8, Fesoterodine fumarate 385367-47-5, Tarafenacin 823178-28-5 862189-96-6
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(orally disintegrating porous film comprising pharmacol. active substance and its manufg. method)
IT 170729-80-3, Aprepitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(orally disintegrating porous film comprising pharmacol. active

substance and its manufg. method)
RN 170729-80-3 CAPLUS
CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (4 CITINGS)

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
CN 105873572 A	CN 2014-80071821	Register|Global Dossier
EP 3069716 A1	EP 2014-861454	Register|Federated Reg.
KR 1407922 B1	KR 2013-138040	Register|Global Dossier
US 20160279071 A1	US 2016-15036784	Register|Global Dossier
WO 2015072684 A1	WO 2014-KR10293	Register|Global Dossier

L5 ANSWER 43 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2014:38255 CAPLUS Full-text
DOCUMENT NUMBER: 160:166366
TITLE: Preparation of stable injectable pharmaceutical compositions of neurokinin 1 receptor antagonist
INVENTOR(S): Karavas, Evangelos; Koutris, Efthimos; Bikiaris, Dimitrios; Chatidou, Sotiria; Diakidou, Amalia; Barmpalexis, Panagiotis; Konstanti, Louiza; Minioti, Katerina
PATENT ASSIGNEE(S): Pharmathen S.A., Greece
ULTIMATE OWNER: PARTNERS GROUP HOLDING AG
ULTIMATE OWNER STANDARD: Partners Group
SOURCE: PCT Int. Appl., 24pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2014005606	A1	20140109	WO 2012-EP2854	20120706
EP 2866797	A1	20150506	EP 2012-756353	20120706
EP 2866797	B1	20200429		
RS 60599	B1	20200831	RS 2020-846	20120706
ES 2798103	T3	20201209	ES 2012-756353	20120706
US 20150165045	A1	20150618	US 2014-14412147	20141230
US 20200237920	A1	20200730	US 2020-16851779	20200417

PRIORITY APPLN. INFO.:

EP 2012-756353	A3	20120706
WO 2012-EP2854	W	20120706
US 2014-14412147	A1	20141230

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE

WO 2014005606	A1	Dead	20201202
EP 2866797	A1	Indeterminate	20201106
EP 2866797	B1	Indeterminate	20201107
RS 60599	B1	Alive	20201121
ES 2798103	T3	Alive	20201217
US 20150165045	A1	Dead	20220105
US 20200237920	A1	Dead	20231109

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OTHER SOURCE(S): CASFORMULTNS 2014:38255

AB The present invention relates to a controlled release sterile injectable formulation in the form of soln., suspension or sol-gel formulation for i.m. or s.c. administration comprising a therapeutically effective amt. of a neurokinin 1 receptor antagonist, in particular aprepitant or fosaprepitant or pharmaceutical acceptable salts, derivs. or metabolites thereof. It also relates to a process for developing such formulations. Thus, an aq. ready-to-use soln. comprised fosaprepitant dimeglumine 142.7, and HPMC-K100 6.7 g/L and water for injection qs to 1 L.

IPCI A61K0031-165 [I]; A61K0009-00 [I]

IPCR A61K0009-00 [I]; A61K0031-165 [I]

CC 63-6 (Pharmaceuticals)

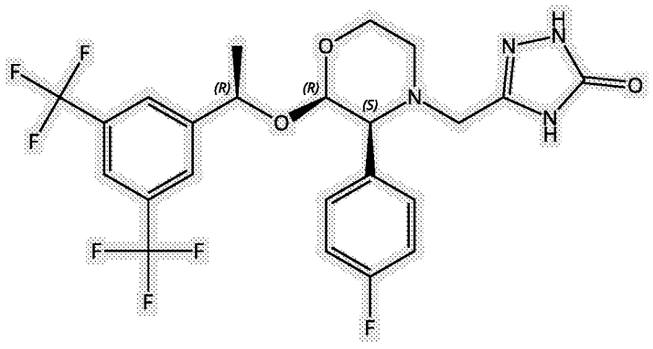
IT Castor oil
Cottonseed oil
Gelatins
Lecithins
Polymers
Polyoxyalkylenes
Sesame oil
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. of stable injectable pharmaceutical compns. of neurokinin 1 receptor antagonist)

IT 170729-80-3, Aprepitant 172673-20-0 265121-04-8, Fosaprepitant dimeglumine
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. of stable injectable pharmaceutical compns. of neurokinin 1 receptor antagonist)

IT 170729-80-3, Aprepitant
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. of stable injectable pharmaceutical compns. of neurokinin 1 receptor antagonist)

RN 170729-80-3 CAPLUS

CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

OS.CITING REF COUNT: 4 THERE ARE 4 CAPLUS RECORDS THAT CITE THIS RECORD (4 CITINGS)

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

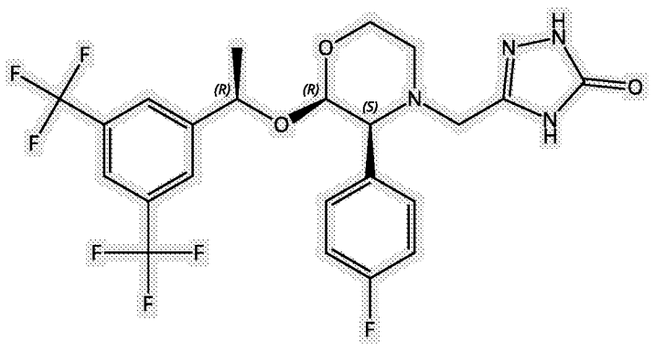
LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
EP 2866797 A1	EP 2012-756353	Register|Federated Reg.
EP 2866797 B1	EP 2012-756353	Register|Federated Reg.
ES 2798103 T3	ES 2012-756353	Register
RS 60599 B1	RS 2020-846	Register
US 20150165045 A1	US 2014-14412147	Register|Global Dossier
US 20200237920 A1	US 2020-16851779	Register|Global Dossier
WO 2014005606 A1	WO 2012-EP2854	Register|Global Dossier

L5 ANSWER 44 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2013:496643 CAPLUS Full-text
DOCUMENT NUMBER: 159:140262
TITLE: Preparation of aprepitant emulsion for intravenous injection
AUTHOR(S): Zhou, Wei; Chen, Fei; Chen, Ning; Mao, Ke
CORPORATE SOURCE: School of Pharmaceutical, Jiangsu Provincial Institute of Materia Medica, Nanjing University of Technology, Nanjing, Jiangsu Province, 211816, Peop. Rep. China
SOURCE: Zhongguo Yiyao Gongye Zazhi (2012), 43(12), 1003-1006
CODEN: ZYGZEA; ISSN: 1001-8255
PUBLISHER: Zhongguo Yiyao Gongye Zazhi Bianjibu
DOCUMENT TYPE: Journal
LANGUAGE: Chinese

AB The formulation of aprepitant emulsion for i.v. injection was optimized by single factor test and orthogonal design. The properties, such as appearance, particle size, ζ potential and stability of the product were investigated. The results showed that the type and amt. of emulsifier as well as the amt. of oleic acid had the greater effect on stability. The optimal formulation of aprepitant emulsion was as follows: aprepitant was 0.25%, soybean oil was 15%, egg yolk lecithin ESO was 2.5% and oleic acid was 0.125%. The appearance of the product was ivory. The av. particle size, PDI, centrifugal stability const. (Ke), ζ potential, pH value and drug content of the product before and after sterilization were (215.71±1.26) and (220.3±0.53) nm, 0.203±0.016 and 0.210±0.009, 0.21±0.01 and 0.34±0.01, (-37.5±0.2) and (-37.6±0.5) mV, 7.21±0.23 and 7.31±0.30, (101.03±0.89)% and (101.12±1.20)%, resp.

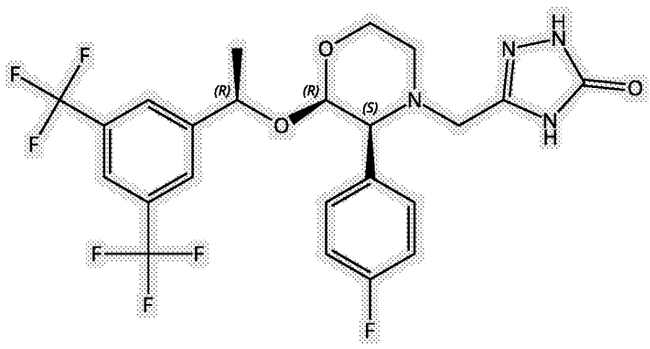
CC 63-6 (Pharmaceuticals)
IT Egg yolk lecithins
Soybean oil
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(prepn. of aprepitant emulsion for i.v. injection)
IT 170729-80-3, Aprepitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. of aprepitant emulsion for i.v. injection)
IT 170729-80-3, Aprepitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. of aprepitant emulsion for i.v. injection)
RN 170729-80-3 CAPLUS
CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

L5 ANSWER 45 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2010:1100829 CAPLUS Full-text
DOCUMENT NUMBER: 153:415489
TITLE: Simulating Fasted Human Intestinal Fluids: Understanding the Roles of Lecithin and Bile Acids
AUTHOR(S): Soederlind, Erik; Karlsson, Eva; Carlsson, Anders; Kong, Rui; Lenz, Anna; Lindborg, Sara; Sheng, Jennifer J.
CORPORATE SOURCE: Pharmaceutical Development, AstraZeneca, Moelndal, Swed.
SOURCE: Molecular Pharmaceutics (2010), 7(5), 1498-1507
CODEN: MPOHBP; ISSN: 1543-8384
DIGITAL OBJECT ID: 10.1021/mp100144v
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The purpose of this work is to evaluate the roles of lecithin and bile salts in a new generation of fasted simulated small intestinal fluid (FaSSIF-II), thus enhancing the closer mimic of simulated fluids to the real human intestinal fluids (HIF) in drug discovery and drug product development. To assess the effects of lecithin in FaSSIF-II, soly. studies were conducted at 37 °C using four media including first generation simulated intestinal fluid (FaSSIF-I), FaSSIF-II, phosphate pH 6.5 buffer, and HIF. A total of 24 model compds. representing a wide range of biopharmaceutic properties were included. The drug soly. values measured in the FaSSIF-II were compared with those in FaSSIF-I, pH 6.5 buffer and HIF. To assess the effects of bile acids, soly. was measured for 4 compds. in the FaSSIF-I contg. five different bile acids of various concns. The lecithin concn. in the FaSSIF-II is lowered from 0.75 mM to 0.2 mM. The results suggested that the FaSSIF-II is a better medium to reflect HIF, compared with pH 6.5 phosphate buffer and FaSSIF-I. Soly. of neutral compds. including atovaquone, carbamazepine, cyclosporine, danazol, diethylstilbestrol, felodipine, griseofulvin and probucol in FaSSIF-II showed improvement in predicting the in vivo soly. The relative std. deviation (SD) of soly. measurement in FaSSIF-II is comparable with FaSSIF-I. For the acidic and basic tested compds., the FaSSIF-II performs similarly to the FaSSIF-I. Exptl. results showed that the level of bile salts typically is less than 5 mM under fasted state. Among the five studied bile acids, the conjugation (glycine or taurine) has no impact on the drug solubilization, while there may be a minimal effect of the degree of hydroxylation of the steroid ring system on solubilization. The lecithin concn. of 0.2 mM in FaSSIF-II has been demonstrated to closely represent HIF, for both neutral and ionizable compds. In the compn. of simulated intestinal fluids, the structure of bile acids has minimal effect, providing the flexibility of choosing one bile salt to represent complex in vivo bile acids.
CC 63-5 (Pharmaceuticals)
ST intestine fluid human lecithin bile acid drug soly
IT Artificial intestinal juice
Dissolution
Human
Hydroxylation
Intestinal juice
Solubility
Solubilization
(simulating fasted human intestinal fluids, roles of lecithin and bile acids)
IT Bile acids
Egg yolk lecithins
Phosphatidylcholines
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(simulating fasted human intestinal fluids, roles of lecithin and bile acids)
IT 81-24-3, Taurocholic acid 145-42-6, Sodium taurocholate 360-65-6, Glycodeoxycholic acid 475-31-0, Glycocholic acid 516-50-7, Taurodeoxycholic acid 640-79-9, Glycochenodeoxycholic acid
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(simulating fasted human intestinal fluids, roles of lecithin and bile acids)

IT 56-53-1, Diethylstilbestrol 57-66-9, Probenecid 58-32-2, Dipyridamole
68-26-8, Retinol 81-81-2, Warfarin 126-07-8, Griseofulvin 298-46-4,
Carbamazepine 530-78-9, Flufenamic acid 599-79-1, Sulfasalazine
1951-25-3, Amiodarone 15307-86-5, Diclofenac 17230-88-5, Danazol
23288-49-5, Probucol 29094-61-9, Glipizide 36322-90-4, Piroxicam
50679-08-8, Terfenadine 51803-78-2, Nimesulide 59865-13-3, Cyclosporin
A 65277-42-1, Ketoconazole 72509-76-3, Felodipine 72956-09-3,
Carvedilol 95233-18-4, Atovaquone 138402-11-6, Irbesartan
168273-06-1, Rimonabant 170729-80-3, Aprepitant
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES
(Uses)
(simulating fasted human intestinal fluids, roles of lecithin
and bile acids)
IT 170729-80-3, Aprepitant
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES
(Uses)
(simulating fasted human intestinal fluids, roles of lecithin
and bile acids)
RN 170729-80-3 CAPLUS
CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phen
yl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX
NAME)



Absolute stereochemistry shown
Rotation (+)

OS.CITING REF COUNT: 25 THERE ARE 25 CAPLUS RECORDS THAT CITE THIS
RECORD (25 CITINGS)
REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 46 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2006:142759 CAPLUS Full-text
DOCUMENT NUMBER: 144:239925
TITLE: Solid carriers for improved delivery of active
ingredients containing surfactants and glycerides
INVENTOR(S): Patel, Mahesh
PATENT ASSIGNEE(S): USA
ULTIMATE OWNER: LIPOCINE INC.
ULTIMATE OWNER STANDARD: Lipocine
SOURCE: U.S. Pat. Appl. Publ., 35 pp., Cont.-in-part of U.S.
Ser. No. 428,341.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 13
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20060034937	A1	20060216	US 2005-196805	20050802
US 6248363	B1	20010619	US 1999-447690	19991123
CA 2706113	A1	20010531	CA 2000-2706113	20001122
US 20030064097	A1	20030403	US 2001-800593	20010306
US 6569463	B2	20030527		

US 20030215496	A1	20031120	US 2003-428341		20030501
US 6923988	B2	20050802			
WO 2007018943	A2	20070215	WO 2006-US27159		20060712
WO 2007018943	A3	20090507			
US 20090074859	A1	20090319	US 2008-326711		20081202
JP 2012116863	A	20120621	JP 2012-29635		20120214
US 20140357586	A1	20141204	US 2014-14460188		20140814
US 20150224130	A9	20150813			
US 20150273067	A1	20151001	US 2015-14713692		20150515
US 20180125978	A1	20180510	US 2017-15625764		20170616
US 20200061191	A1	20200227	US 2019-16289565		20190228
US 20210008212	A1	20210114	US 2020-16917731		20200630
PRIORITY APPLN. INFO.:			US 1999-447690	A3	19991123
			US 2001-800593	A1	20010306
			US 2003-428341	A2	20030501
			CA 2000-2391923	A3	20001122
			JP 2001-539423	A3	20001122
			US 2002-159601	A2	20020530
			US 2005-196805	A	20050802
			US 2008-326711	A1	20081202
			US 2014-14460188	A1	20140814
			US 2017-15625764	A1	20170616
			US 2019-16289565	A1	20190228

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
US 20060034937	A1	Dead	20201107
US 6248363	B1	Dead	20201107
CA 2706113	A1	Dead	20201121
US 20030064097	A1	Dead	20201106
US 6569463	B2	Dead	20201106
US 20030215496	A1	Dead	20201106
US 6923988	B2	Dead	20201107
WO 2007018943	A2	Dead	20201201
WO 2007018943	A3	Dead	20201201
US 20090074859	A1	Dead	20201107
JP 2012116863	A	Alive	20201121
US 20140357586	A1	Dead	20201107
US 20150224130	A9	Dead	20201107
US 20150273067	A1	Dead	20201107
US 20180125978	A1	Dead	20201106
US 20200061191	A1	Dead	20201106
US 20210008212	A1	Dead	20210128

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OTHER SOURCE(S): CASFORMULTNS 2006:142759

AB The present invention provides solid pharmaceutical compns. for improved delivery of a wide variety of pharmaceutical active ingredients contained therein or sep. administered. In one embodiment, the solid pharmaceutical compn. includes a solid carrier, the solid carrier including a substrate and an encapsulation coat on the substrate. The encapsulation coat can include different combinations of pharmaceutical active ingredients, hydrophilic surfactant, lipophilic surfactants and triglycerides. In another embodiment, the solid pharmaceutical compn. includes a solid carrier, the solid carrier being formed of different combinations of pharmaceutical active ingredients, hydrophilic surfactants, lipophilic surfactants and triglycerides. The compns. of the present invention can be used for improved delivery of hydrophilic or hydrophobic pharmaceutical active ingredients, such as drugs, nutritional agents, cosmeceuticals and diagnostic agents. For example, particles contained glyburide, PEG stearate, glycerol monolaurate, and Nonpareil seed.

INCL 424497000

IPCI A61K0009-50 [I]; A61K0009-16 [I]

IPCR A61K0009-50 [I]; A61K0009-16 [I]

NCL 424/497.000

CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 18, 62

IT Lecithins
RL: COS (Cosmetic use); FFD (Food or feed use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hydrogenated; solid carriers for improved delivery of active ingredients contg. surfactants and glycerides)

IT Diglycerides

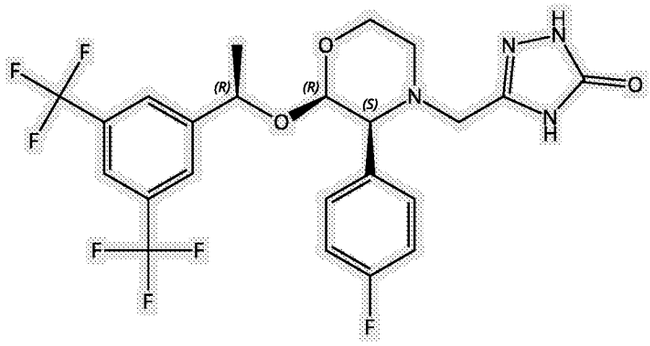
Ethoxylated hydrogenated castor oil
Glycerides
Lecithins
Oligopeptides
Peptides
Polyoxyalkylenes
Safflower oil
Sterols
RL: COS (Cosmetic use); FFD (Food or feed use); THU (Therapeutic use);
BIOL (Biological study); USES (Uses)
(solid carriers for improved delivery of active ingredients contg. surfactants and glycerides)

IT 50-35-1, Thalidomide 50-49-7, Imipramine 52-01-7, Spironolactone
52-86-8, Haloperidol 53-03-2, Prednisone 53-39-4, Oxandrolone
57-83-0, Progesterone, biological studies 67-20-9, Nitrofurantoin
81-24-3 83-44-3, Deoxycholic acid 87-69-4D, Tartaric acid, esters
112-80-1, 9-Octadecenoic acid (9Z)-, biological studies 124-07-2,
Octanoic acid, biological studies 145-42-6, Sodium taurocholate
151-41-7, Lauryl sulfate 302-79-4, Tretinoin 303-98-0, Coenzyme Q10
321-64-2, Tacrine 334-48-5, Decanoic acid 357-70-0, Galantamine
511-12-6, Dihydroergotamine 541-15-1D, Carnitine, analogs and derivs.
577-11-7, Sodium docusate 595-33-5, Megestrol acetate 1622-61-3,
Clonazepam 1972-08-3, Dronabinol 2644-64-6, DPPC 5633-20-5,
Oxybutynin 5786-21-0, Clozapine 5949-44-0, Testosterone undecanoate
9002-96-4 9003-39-8, PVP K30 9004-65-3, Hydroxypropyl methylcellulose
9004-96-0, Crodet O 100 9005-32-7D, Alginic acid, salts 9005-37-2,
Propylene glycol alginate 9005-38-3, Sodium alginate 9005-63-4,
Polyoxyethylene sorbitan 9005-64-5, PEG sorbitan monolaurate
9005-65-6, PEG sorbitan monooleate 9009-32-9, Polyglyceryl stearate
10041-19-7 10238-21-8, Glyburide 10540-29-1, Tamoxifen 11140-04-8,
Imwitor 988 14440-80-3, Stearyl lactylate 18656-38-7, DMPC
21256-18-8, Oxaprozin 25086-15-1, Eudragit L100 25322-68-3,
Polyethylene glycol 25322-68-3D, esters 25618-55-7, Polyglycerol
26545-74-4 27215-38-9, Monomuls 90-45 28721-07-5, Oxacarbazepine
29975-16-4, Estazolam 31566-31-1, Imwitor 191 34911-55-2, Bupropion
37220-82-9, Peceol 47931-85-1, Salmon calcitonin 49562-28-9,
Fenofibrate 51322-75-9, Tizanidine 51333-22-3, Budesonide
53123-88-9, Sirolimus 55142-85-3, Ticlopidine 63675-72-9, Nisoldipine
68475-42-3, Anagrelide 70458-96-7, Norfloxacin 71125-38-7, Meloxicam
72509-76-3, Felodipine 72956-09-3, Carvedilol 73590-58-6, Omeprazole
73963-72-1, Cilostazol 74504-64-6, Polyglyceryl laurate 75330-75-5,
Lovastatin 75695-93-1, Isradipine 77337-76-9, Acamprosate
79902-63-9, Simvastatin 81103-11-9, Clarithromycin 82410-32-0,
Ganciclovir 84057-84-1, Lamotrigine 84449-90-1, Raloxifene
84625-61-6, Itraconazole 87333-19-5, Ramipril 88150-42-9, Amlodipine
91374-21-9, Ropinirole 100427-26-7, Lercanidipine 100986-85-4,
Levofloxacin 103577-45-3, Lansoprazole 104987-11-3, Tacrolimus
106266-06-2, Risperidone 106308-44-5, Rufinamide 106392-12-5,
Oxyethylene-oxypropylene block copolymer 107724-20-9, Eplerenone
107753-78-6, Zafirlukast 111025-46-8, Pioglitazone 112811-59-3,
Gatifloxacin 115103-54-3, Tiagabine 124937-51-5, Tolterodine
127779-20-8, Saquinavir 127829-97-4, Solulan C-24 129318-43-0,
Alendronate sodium 129722-12-9, Aripiprazole 130929-57-6, Entacapone
132539-06-1, Olanzapine 133040-01-4, Eprosartan 134308-13-7, Tolcapone
134523-00-5, Atorvastatin 137862-53-4, Valsartan 139755-83-2,
Sildenafil 145158-71-0, Tegaserod 146478-45-7, Polyglycerol dioleate
146939-27-7, Ziprasidone 147536-97-8, Bosentan 154598-52-4, Efavirenz
156259-68-6, Capmul MCM 162011-90-7, Rofecoxib 169590-42-5, Celecoxib
170729-80-3, Aprepitant 174392-00-8, Polyglyceryl monooleate
197179-53-6, Nonpareil
RL: COS (Cosmetic use); FFD (Food or feed use); THU (Therapeutic use);
BIOL (Biological study); USES (Uses)
(solid carriers for improved delivery of active ingredients contg. surfactants and glycerides)

IT 170729-80-3, Aprepitant
RL: COS (Cosmetic use); FFD (Food or feed use); THU (Therapeutic use);
BIOL (Biological study); USES (Uses)
(solid carriers for improved delivery of active ingredients contg. surfactants and glycerides)

RN 170729-80-3 CAPLUS
CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phen
yl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX

NAME)



Absolute stereochemistry shown
Rotation (+)

OS.CITING REF COUNT: 162 THERE ARE 162 CAPLUS RECORDS THAT CITE THIS RECORD (272 CITINGS)

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
CA 2706113 A1	CA 2000-2706113	Register
JP 2012116863 A	JP 2012-29635	Register|Global Dossier
US 6248363 B1	US 1999-447690	Register
US 20030064097 A1	US 2001-800593	Register
US 6569463 B2	US 2001-800593	Register
US 20030215496 A1	US 2003-428341	Register|Global Dossier
US 6923988 B2	US 2003-428341	Register|Global Dossier
US 20060034937 A1	US 2005-196805	Register|Global Dossier
US 20090074859 A1	US 2008-326711	Register|Global Dossier
US 20140357586 A1	US 2014-14460188	Register|Global Dossier
US 20150224130 A9	US 2014-14460188	Register|Global Dossier
US 20150273067 A1	US 2015-14713692	Register|Global Dossier
US 20180125978 A1	US 2017-15625764	Register|Global Dossier
US 20200061191 A1	US 2019-16289565	Register|Global Dossier
US 20210008212 A1	US 2020-16917731	Register|Global Dossier
WO 2007018943 A2	WO 2006-US27159	Register|Global Dossier
WO 2007018943 A3	WO 2006-US27159	Register|Global Dossier

L5 ANSWER 47 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2005:1311702 CAPLUS Full-text
DOCUMENT NUMBER: 144:57525
TITLE: Coated vaginal devices for vaginal delivery of therapeutically effective and/or health-promoting agents
INVENTOR(S): Wilson, Michelle; Desai, Kishorkumar J.; Pauletti, Giovanni M.; Antoon, Mitchell K.; Clendening, Chris E.
PATENT ASSIGNEE(S): UMD, Inc., USA
ULTIMATE OWNER: U M D
ULTIMATE OWNER STANDARD: U M D
SOURCE: U.S. Pat. Appl. Publ., 40 pp., Cont.-in-part of U.S. Ser. No. 126,863
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 12
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20050276836	A1	20051215	US 2005-180076	20050712
US 6197327	B1	20010306	US 1998-79897	19980515
US 6086909	A	20000711	US 1999-249963	19990212
US 6572874	B1	20030603	US 2000-626025	20000727
NZ 508130	A	20020301	NZ 2000-508130	20001113

AU 2001054192	A	20010913	AU 2001-54192		20010703
AU 765269	B2	20030911			
US 20030049302	A1	20030313	US 2002-226667		20020821
US 6982091	B2	20060103			
US 20040005345	A1	20040108	US 2003-349029		20030122
US 6905701	B2	20050614			
US 20040043071	A1	20040304	US 2003-600849		20030620
US 20050249774	A1	20051110	US 2005-126863		20050510
US 7744916	B2	20100629			
PRIORITY APPLN. INFO.:			US 1997-60049325	P	19970611
			US 1998-79897	A2	19980515
			US 1999-249963	A2	19990212
			US 2000-626025	A2	20000727
			US 2002-226667	A2	20020821
			US 2003-349029	A2	20030122
			US 2003-600849	A2	20030620
			US 2004-60587454	P	20040712
			US 2005-126863	A2	20050510
			AU 1998-76976	A3	19980610
			NZ 1998-502120	A1	19980610
			US 1999-249693	A2	19990212
			US 1999-60146218	P	19990728
			US 2001-60315877	P	20010829
			US 2002-60390748	P	20020621

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
US 20050276836	A1	Dead	20201107
US 6197327	B1	Dead	20201107
US 6086909	A	Dead	20201106
US 6572874	B1	Dead	20201107
NZ 508130	A	Dead	20201121
AU 2001054192	A	Dead	20201107
AU 765269	B2	Dead	20201106
US 20030049302	A1	Dead	20201121
US 6982091	B2	Dead	20201121
US 20040005345	A1	Dead	20201107
US 6905701	B2	Dead	20201107
US 20040043071	A1	Dead	20201121
US 20050249774	A1	Dead	20220310
US 7744916	B2	Dead	20220310

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OTHER SOURCE(S): CASFORMULTNS 2005:1311702

AB Disclosed is a vaginal device for delivering therapeutical and/or health-promoting agents. The vaginal device partly or completely coated by, covered by or combined with a coating or covering comprising a film, foam, strip, cap, cup or particles. The coating of the device comprises a mucoadhesive compn. comprising a therapeutical and/or health-promoting agent. For example, sumatriptan vaginal suppository were prepd. from Suppocire AS2X, hydroxypropyl Me cellulose as a mucoadhesive agent, and Transcutol as a permeation enhancer.

INCL 424422000

IPCI A61F0013-00 [ICM,7]

IPCR A61F0013-00 [I]; A61K0009-00 [I]; A61K0009-02 [I]; A61K0009-12 [I]; A61K0009-19 [I]; A61K0009-70 [I]

NCL 424/422.000

CC 63-6 (Pharmaceuticals)

IT Alkaloids
Amino acids
Bile salts
Cellulosic fibers
Coenzymes
Cottonseed oil
Essential oils
Fats and Glyceridic oils
Interleukins
Lecithins
Minerals
Natural products, pharmaceutical
Peptides
Phenols
Polyketides

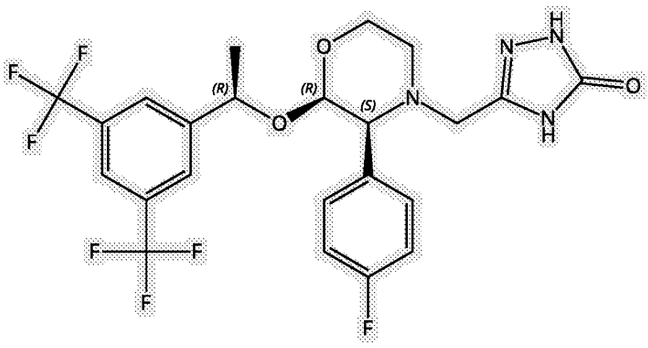
Polyoxyalkylenes
Proteins
Resins
Silicone rubber
Tannins
Terpenes
Vitamins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(coated vaginal devices for vaginal delivery of therapeutically effective and/or health-promoting agents)

IT 68379-02-2, Clofilium 69655-05-6, Didanosine 70458-96-7, Norfloxacin 71048-87-8, Levonantradol 71125-38-7, Meloxicam 72479-26-6, Fenticonazole 72509-76-3, Felodipine 73573-87-2, Formoterol 74103-06-3, Ketorolac 74103-07-4, Ketorolac tromethamine 74191-85-8, Doxazosin 74545-79-2, Aloeresin A 75088-80-1, Manoalide 75330-75-5, Lovastatin 75695-93-1, Isradipine 76584-70-8, Divalproex sodium 79350-37-1, Cefixime 79778-41-9, Neridronate 80210-62-4, Cefpodoxime 80937-31-1, Flosulide 82410-32-0, Ganciclovir 83905-01-5, Azithromycin 83991-25-7, Ambasilide 84625-61-6, Itraconazole 85622-93-1, Temozolomide 85721-33-1, Ciprofloxacin 86386-73-4, Fluconazole 88150-42-9, Amlodipine 89365-50-4, Salmeterol 89565-68-4, Tropisetron 89778-26-7, Toremifene 89987-06-4, Tiludronate 90357-06-5, Bicalutamide 90961-53-8, Tedisamil 91714-94-2, Bromfenac 92665-29-7, Cefprozil 95058-81-4, Gemcitabine 95298-47-8 95751-30-7, Charybdotoxin 97240-79-4, Topiramate 97682-44-5, Irinotecan 98079-51-7, Lomefloxacin 98225-48-0, Brevetoxin 99614-02-5, Ondansetron 101526-83-4, Sematilide 103628-46-2, Sumatriptan 104227-87-4, Famciclovir 105462-24-6 107868-30-4, Exemestane 110042-95-0, Acemannan 112455-84-2, Papuamine 112809-51-5, Letrozole 114084-78-5, Ibandronate 114977-28-5, Docetaxel 115256-11-6, Dofetilide 115956-12-2, Dolasetron 118072-93-8, Zoledronate 120511-73-1, Anastrozole 121368-58-9, Olpadronate 121679-13-8, Naratriptan 122647-31-8, Ibutilide 123948-87-8, Topotecan 127779-20-8, Saquinavir 129618-40-2, Nevirapine 132539-06-1, Olanzapine 134678-17-4, Lamivudine 135729-61-2, Palonosetron 136470-78-5, Abacavir 136817-59-9, Delavirdine 137234-62-9, Voriconazole 139110-80-8, Zanamivir 139226-28-1, Darbufelone 139264-17-8, Zolmitriptan 143322-58-1, Eletriptan 143491-57-0, Emtricitabine 144034-80-0, Rizatriptan 147127-20-6, Tenofovir 149908-53-2, Azimilide 150378-17-9, Indinavir 152459-95-5, Imatinib 153559-49-0, Bexarotene 154323-57-6, Almotriptan 154361-50-9, Capecitabine 154598-52-4, Efavirenz 155213-67-5, Ritonavir 158751-64-5, ClAmikalant 159519-65-0, Enfuvirtide 159989-64-7, Nelfinavir 161814-49-9, Amprenavir 162011-90-7, Rofecoxib 169590-42-5, Celecoxib 169944-35-8, Bisulfan 170729-80-3, Aprepitant 181695-72-7, Valdecoxib 184475-35-2, Gefitinib 190017-00-6, Correolide 192725-17-0, Lopinavir 196618-13-0, Oseltamivir 198470-84-7, Parecoxib 198904-31-3, Atazanavir 202409-33-4, Etoricoxib 220991-20-8, Lumiracoxib 226700-79-4, Fosamprenavir 260792-29-8, 6β,7β-Diacetoxy-13-hydroxylabda-8,14-diene 264875-61-8, Cimiracemoside A 501938-01-8, 23-epi-26-Deoxyactein 856012-03-8 865111-98-4 865147-59-7, Altissinone 871260-93-4
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(coated vaginal devices for vaginal delivery of therapeutically effective and/or health-promoting agents)

IT 170729-80-3, Aprepitant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(coated vaginal devices for vaginal delivery of therapeutically effective and/or health-promoting agents)

RN 170729-80-3 CAPLUS

CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

OS.CITING REF COUNT: 23 THERE ARE 23 CAPLUS RECORDS THAT CITE THIS RECORD (23 CITINGS)

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
AU 2001054192 A	AU 2001-54192	Register
AU 765269 B2	AU 2001-54192	Register
NZ 508130 A	NZ 2000-508130	Register
US 6197327 B1	US 1998-79897	Register
US 6086909 A	US 1999-249963	Register
US 6572874 B1	US 2000-626025	Register
US 20030049302 A1	US 2002-226667	Register
US 6982091 B2	US 2002-226667	Register
US 20040005345 A1	US 2003-349029	Register|Global Dossier
US 6905701 B2	US 2003-349029	Register|Global Dossier
US 20040043071 A1	US 2003-600849	Register|Global Dossier
US 20050249774 A1	US 2005-126863	Register|Global Dossier
US 7744916 B2	US 2005-126863	Register|Global Dossier
US 20050276836 A1	US 2005-180076	Register|Global Dossier

L5 ANSWER 48 OF 48 CAPLUS COPYRIGHT 2024 ACS on STN
ACCESSION NUMBER: 2002:695760 CAPLUS Full-text
DOCUMENT NUMBER: 137:237717
TITLE: Inhalant compositions containing anticholinergics and NK1 receptor antagonists
INVENTOR(S): Meade, Christopher John Montague; Pairet, Michel; Pieper, Michael Paul
PATENT ASSIGNEE(S): Boehringer Ingelheim Pharma K.-G., Germany
SOURCE: PCT Int. Appl., 42 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 14
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002069944	A2	20020912	WO 2002-EP1987	20020226
WO 2002069944	A3	20031002		
DE 10111058	A1	20020912	DE 2001-10111058	20010308
CA 2439915	A1	20020912	CA 2002-2439915	20020226
AU 2002251010	A1	20020919	AU 2002-251010	20020226
EP 1370293	A2	20031217	EP 2002-719915	20020226
JP 2004519484	T	20040702	JP 2002-569121	20020226
MX 2003008051	A	20031204	MX 2003-8051	20030905

PRIORITY APPLN. INFO.:
DE 2001-10111058 A 20010308
WO 2002-EP1987 W 20020226

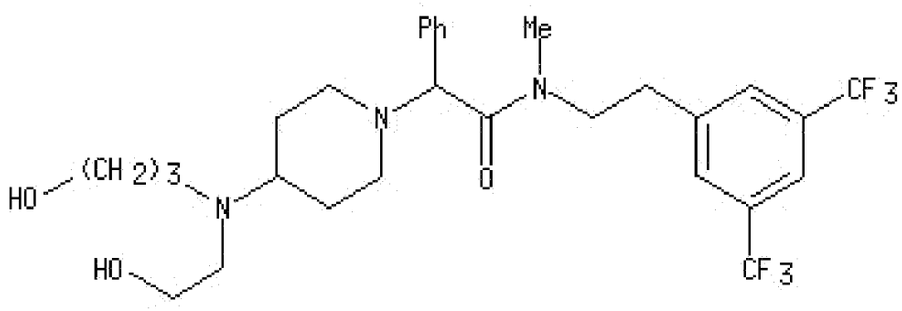
PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
WO 2002069944	A2	Dead	20201201

WO 2002069944	A3	Dead	20201201
DE 10111058	A1	Dead	20201121
CA 2439915	A1	Dead	20201121
AU 2002251010	A1	Dead	20201121
EP 1370293	A2	Dead	20201202
JP 2004519484	T	Dead	20220303
MX 2003008051	A	Dead	20201121

OTHER SOURCE(S): MARPAT 137:237717; CASFORMULTNS 2002:695760

GI



AB The invention relates to drug compns. based on anticholinergics and on NK1 receptor antagonists, to methods for their prodn., and to their use as inhalants for the treatment of respiratory tract diseases. Synthesis of NK1 receptor antagonists from the group of bis-trifluoromethyl-phenyl-piperidine derivs. are described. The products are used in suspension aerosols. Thus a compn. contained (wt./wt.%): tiotropium bromide 0.015; NK1 receptor antagonist 0.066; soy lecithin 0.2; TG11: TG12 = 2:3 to 100.

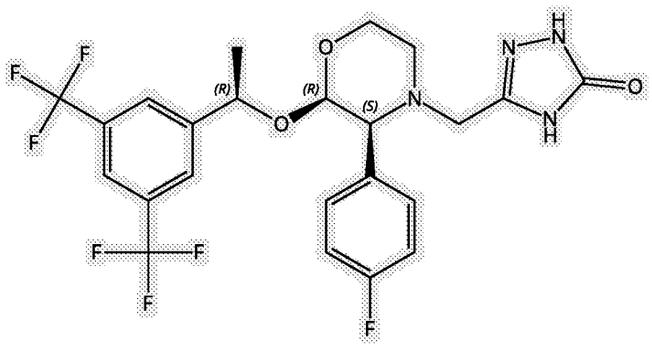
IPCI A61K0031-00 [ICM,7]

IPCR A61K0009-08 [I]; A61K0009-00 [I]; A61K0009-10 [I]; A61K0009-14 [I]; A61K0009-48 [I]; A61K0009-72 [I]; A61K0031-00 [I]; A61K0031-223 [I]; A61K0031-403 [I]; A61K0031-439 [I]; A61K0031-4468 [I]; A61K0031-46 [I]; A61K0031-4745 [I]; A61K0031-535 [I]; A61K0031-55 [I]; A61K0045-06 [I]; A61K0047-04 [I]; A61K0047-10 [I]; A61K0047-12 [I]; A61K0047-18 [I]; A61K0047-22 [I]; A61K0047-26 [I]; A61P0011-00 [I]; A61P0011-08 [I]; A61P0029-00 [I]; A61P0043-00 [I]

CC 63-6 (Pharmaceuticals)

IT 50-81-7, Ascorbic acid, biological studies 56-81-5, Glycerol, biological studies 57-55-6, Propylene glycol, biological studies 64-02-8 64-17-5, Ethanol, biological studies 64-18-6, Formic acid, biological studies 64-19-7, Acetic acid, biological studies 65-85-0, Benzoic acid, biological studies 74-98-6, n-Propane, biological studies 75-28-5, Isobutane 77-92-9, Citric acid, biological studies 79-09-4, Propionic acid, biological studies 106-97-8, n-Butane, biological studies 110-15-6, Succinic acid, biological studies 110-16-7, Maleic acid, biological studies 110-17-8, Fumaric acid, biological studies 123-03-5, Cetylpyridinium chloride 431-89-0, TG227 526-83-0, Tartaric acid 811-97-2, TG134a 1406-18-4, Vitamin E 6915-15-7, Malic acid 7647-01-0, Hydrochloric acid, biological studies 7664-93-9, Sulfuric acid, biological studies 7697-37-2, Nitric acid, biological studies 10035-10-6, Hydrobromic acid, biological studies 11103-57-4, Vitamin A 25322-68-3, Polyethylene glycol 25322-68-3D, alcs. and fatty acid esters 25322-69-4, Polypropylene glycol 60205-81-4, Ipratropium 99571-64-9, Oxitropium 138449-07-7, FK-888 142001-63-6, Saredutant 145742-28-5, CP-122721 147116-64-1, CJ 11974 155418-05-6, SR 140333 168266-90-8, GR 205171 170566-84-4, Lanepitant 170739-80-3, MK-869 171272-39-2, MEN-10930 172673-20-0, L-758298 173941-19-0, YM 49244 173941-22-5, YM 35375 173941-74-7, YM 44778 174636-32-9, SB 223412 174661-97-3, DA-5018 178370-50-8, MDL 103896 183747-35-5, Nepadutant 188241-50-1, S-19752 193694-35-8, MDL-105172A 201152-86-5, SR-144190 206052-25-7, MEN-11149 209474-01-1, Neuronorm 214487-46-4, MEN-11467 217185-75-6, TAK-637 350610-25-2 350610-26-3, 6b-I 350610-27-4, DNK-33A 350610-29-6, ZM-274773 350610-34-3, DNK 333A 350610-51-4, CGP 60829 350610-61-6, NKP 608A 350610-64-9, NKP 608C 415917-13-4 457910-81-5 458568-84-8, TG 11 458569-01-2, TG 12
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(inhalant compns. contg. anticholinergics and NK1 receptor antagonists)
IT 170729-80-3, MK-869
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhalant compns. contg. anticholinergics and NK1 receptor antagonists)
RN 170729-80-3 CAPLUS
CN 3H-1,2,4-Triazol-3-one, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro- (CA INDEX NAME)



Absolute stereochemistry shown
Rotation (+)

OS.CITING REF COUNT: 4 THERE ARE 4 CAPLUS RECORDS THAT CITE THIS RECORD (4 CITINGS)
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
AU 2002251010 A1	AU 2002-251010	Register
CA 2439915 A1	CA 2002-2439915	Register
DE 10111058 A1	DE 2001-10111058	Register
EP 1370293 A2	EP 2002-719915	Register|Federated Reg.
JP 2004519484 T	JP 2002-569121	Register
MX 2003008051 A	MX 2003-8051	Register
WO 2002069944 A2	WO 2002-EP1987	Register|Global Dossier
WO 2002069944 A3	WO 2002-EP1987	Register|Global Dossier

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PE2E SEARCH - Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
L1	17	(A61K9/1075 AND A61K9/0019 AND A61K31/43 AND A61K31/496 AND A61K31/5377 AND A61K47/10 AND A61K47/44)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/03/12 06:53 PM
L2	19	(A61K9/1075 AND A61K9/0019 AND A61K31/496 AND A61K31/5377 AND A61K47/10 AND A61K47/44)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/03/12 06:57 PM
L3	67	(A61K9/1075 AND A61K9/0019 AND A61K31/5377 AND A61K47/10 AND A61K47/44)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/03/12 06:58 PM
L4	1402	(A61K9/1075 AND A61K9/0019 AND A61K47/10 AND	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY,	OR	ON	ON	2024/03/12 06:58 PM

		A61K47/44)	CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)				
L5	31	((A61K9/1075 AND A61K9/0019 AND A61K47/10 AND A61K47/44) AND aprepitant)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/03/12 06:59 PM
L6	3999	(aprepitant AND phospholipid AND oil AND ethanol AND water AND inject$)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/03/12 07:02 PM
L7	31	((("Heron") near3 ("Therapeutics") near3 ("Inc"))).AS,AANM.	(USPAT)	OR	ON	ON	2024/03/12 07:17 PM
L8	83	((("HERON") near3 ("THERAPEUTICS") near3 ("INC"))).AS,AANM.	(US-PGPUB; USPAT)	OR	ON	ON	2024/06/03 08:59 PM

PE2E SEARCH - Search History (Interference)

Ref #	Hits	Search Query	DBs	Default	Plurals	British	Time Stamp

				Operator		Equivalents	
N1	12	(A61K9/1075 AND A61K9/0019 AND A61K31/43 AND A61K31/496 AND A61K31/5377 AND A61K47/10 AND A61K47/44)	(US-PGPUB; USPAT)	OR	ON	ON	2024/03/12 06:55 PM
N2	165	(A61K9/1075 AND A61K9/0019 AND A61K47/10 AND A61K47/44)	(US-PGPUB; USPAT)	OR	ON	ON	2024/03/12 06:59 PM
N3	11	((A61K9/1075 AND A61K9/0019 AND A61K47/10 AND A61K47/44) AND aprepitant)	(US-PGPUB; USPAT)	OR	ON	ON	2024/03/12 07:00 PM
N4	1154	(aprepitant AND phospholipid AND oil AND ethanol AND water AND inject$)	(US-PGPUB; USPAT)	OR	ON	ON	2024/03/12 07:03 PM

METHODS OF USE OF EMULSION FORMULATIONS OF AN NK-1 RECEPTOR ANTAGONIST

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation of U.S. Application No. 18/535,853, filed December 11, 2023, pending, which is a continuation of U.S. Application No. 17/180,593, filed February 19, 2021, now allowed, which is a continuation of U.S. Application No. 16/820,311, filed March 16, 2020, now U.S. Patent No. 11,173,118, which is a continuation of U.S. Application No. 15/965,638, filed April 27, 2018, now U.S. Patent No. 10,624,850, which is a continuation of U.S. Application No. 15/012,532, filed February 1, 2016, now U.S. Patent No. 9,974,742, each of which is incorporated herein in its entirety.

TECHNICAL FIELD

[0002] The disclosure relates generally to emulsion formulations and systems for the intravenous or parenteral administration of an NK-1 receptor antagonist for treatment of emesis. The emulsion formulations are stable for prolonged periods of time. Also described are methods for preparing the stable NK-1 receptor antagonist emulsions and pharmaceutical formulations.

BACKGROUND

[0003] Emesis is a critical problem experienced as a result of anticancer cytotoxic therapy. Up to 80% of patients will experience chemotherapy-induced nausea and vomiting (CINV) without prophylactic therapy (Vieira dos Santos et al., 2012, J Natl Cancer Inst, 104:1280-1292). Navari et al. (1999, N Engl J Med, 340:190-195) showed that neurokinin-1 (NK-1) receptor antagonists improve CINV when used in combination with cisplatin-based chemotherapy. NK-1 receptor antagonists block binding of substance P to the receptor, thereby preventing or limiting induction of vomiting pathways mediated by the NK-1 receptor (Aziz, 2012, Ann Palliat Med, 1:130-136).

[0004] NK-1 receptor antagonists currently approved and marketed include aprepitant and rolapitant HCl, which are both available in oral form. Not surprisingly, oral dosage forms can create a problem for patients suffering from emesis, specifically, for example, on days two and three of chemotherapy. Accordingly, it is desirable to have injectable formulations to simplify treatment for these patients. Described herein are emulsions formulated for administering to a patient by injection. These emulsions are formulated to contain neurokinin-1 receptor antagonists which may be poorly soluble in aqueous solvents or unstable in aqueous-based liquid formulations.

[0005] Liquid formulations containing NK-1 receptor antagonists having poor solubility and/or poor gastrointestinal permeability characteristics can be very challenging to formulate for purposes of long-term storage and for administration. One means of addressing this challenge is to prepare an emulsion which may both allow preparation of an injectable formulation as well as enhance bioavailability of the active agent once administered.

[0006] Intravenous emulsions should have a very small droplet size to circulate in the bloodstream without causing capillary blockage and embolization. These size limits are typified by USP33-NF28 General Chapter <729> for Globule Size Distribution in Lipid Injectable Emulsions, hereinafter referred to as USP <729>, which defines universal limits for (1) mean droplet size not exceeding 500 nm or 0.5 μm and (2) the population of large-diameter fat globules, expressed as the volume-weighted percentage of fat greater than 5 μm (PFAT5) not exceeding 0.05%, irrespective of the final lipid concentration.

[0007] Emulsion formulations must be physically stable. The droplet size limits defined in USP <729> apply throughout the assigned shelf life. All true emulsions are thermodynamically unstable and may over time undergo a range of processes which tend to increase the droplet size. These include direct droplet coalescence, when two droplets collide and form a single new droplet; and aggregation, in which droplets adhere together to form larger masses. Aggregation may in some cases be a precursor of further coalescence into larger droplets. These processes may result in large aggregates rising to the surface of the container, a phenomenon known as 'creaming', and ultimately to free oil being visible on the emulsion surface, known as ‘cracking’.

[0008] Emulsion formulations must also be chemically stable. The drug substance may degrade; for example, lipophilic drugs will partition into the oil phase, which will confer some degree of protection, but hydrolytic degradation may still occur at the oil-water interface. Possible chemical degradation within parenteral fat emulsions includes oxidation of unsaturated fatty acid residues present in triglyceride and lecithin, and hydrolysis of phospholipids leading to the formation of free fatty acids (FFA) and lysophospholipids. Such degradants lower pH, which may then promote further degradation. Thus, pH should be controlled during manufacture and parenteral emulsion formulations may include a buffering agent to provide additional control. Any decrease in pH over the assigned shelf-life may be indicative of chemical degradation.

[0009] In the present application, emulsion formulations were prepared and characterized to identify a formulation and process that will allow an NK-1 receptor antagonist compound to be

incorporated into an emulsion for intravenous injection and remain stable during the shelf life of the formulation.

BRIEF SUMMARY

[0010] The following aspects and embodiments thereof described and illustrated below are meant to be exemplary and illustrative, not limiting in scope.

[0011] In one aspect, a pharmaceutical composition suitable for intravenous administration is provided which comprises a stable emulsion comprising an oil phase, wherein the oil phase comprises a neurokinin 1 (NK-1) receptor antagonist, a surfactant and a co-surfactant; and an aqueous phase, wherein the aqueous phase comprises water, a tonicity agent, and a pH modifier.

[0012] In some embodiments, the NK-1 receptor antagonist is selected from the group consisting of aprepitant, rolapitant, netupitant, lanepitant, vestipitant, orvepitant maleate, casopitant, ezlopitant, serlopitant, befetupitant and maropitant, or a pharmaceutically acceptable salt thereof. In other embodiments, the NK-1 receptor antagonist is poorly soluble in water.

[0013] In some embodiments, the NK-1 receptor antagonist is selected from the group consisting of rolapitant, netupitant, casopitant, ezlopitant, vestipitant, serlopitant, maropitant, and orvepitant.

[0014] In some embodiments, the NK-1 receptor antagonist is not aprepitant.

[0015] In some embodiments, the composition is an oil-in-water emulsion comprising an oil wherein the oil is selected from the group consisting of coconut oil, olive oil, soybean oil, safflower oil, triglycerides, octyl and decyl glycerate, ethyl oleate, glyceryl linoleate, ethyl linoleate, glyceryl oleate, cholesteryl oleate/linoleate or a mixture thereof. In other embodiments, the oil is hydrolyzed. In still other embodiments, the oil is structurally modified.

[0016] In some embodiments, the emulsifier comprises a phospholipid. In another embodiment, the emulsifier is selected from the group consisting of egg phospholipids, soy phospholipids, phosphatidylcholines, phosphatidylethanolamines, phosphatidylserines, phosphatidylglycerols, phosphatidylinositols, phosphatidic acids, mixed chain phospholipids, lysophospholipids, hydrogenated phospholipids, partially hydrogenated phospholipids, and mixtures thereof.

[0017] In some embodiments, the co-surfactant comprises an alcohol. In other embodiments, the co-surfactant is ethanol.

[0018] In some embodiments, the pH modifier comprises an oleate or pharmaceutically acceptable salt thereof. In other embodiments, the oleate is sodium, potassium or ammonium oleate. In yet other embodiments, the pH modifier is sodium oleate or a pharmaceutically acceptable salt thereof.

[0019] In some embodiments, the pH modifier comprises a buffer. In other embodiments, the buffer is selected from the group consisting of phosphate buffer, citrate buffer, Tris buffer, carbonate buffer, succinate buffer, maleate buffer and borate buffer. In still other embodiments, the buffer is selected from the group, phosphate buffered saline (PBS), modified PBS (PBS-mod) and citrate buffer.

[0020] In some embodiments, the pH modifier comprises an oleate and a buffer. In other embodiments, the oleate is sodium oleate and the buffer is Tris buffer.

[0021] In some embodiments, the pH modifier is selected from the group consisting of sodium hydroxide, potassium hydroxide, magnesium hydroxide, sodium carbonate, Tris, sodium linoleate, sodium oleate, potassium oleate, ammonium oleate, potassium carbonate, potassium linoleate, and mixtures thereof.

[0022] In some embodiments, the composition comprises about 5 wt/wt% (weight/weight %) to 15 wt/wt%, 5 wt/wt% to 10 wt/wt%, 7 wt/wt% to 10 wt/wt%, 8 wt/wt% to 9 wt/wt%, or 9 wt/wt% to 10 wt/wt% oil. In another embodiment, the composition comprises about 8 wt/wt5, 8.5 wt/wt%, 9 wt/wt%, 9.5 wt/wt%, 10 wt/wt%, or 10.5 wt/wt% oil. In still other embodiments, the oil is soybean oil.

[0023] In some embodiments, the composition comprises about 10 wt/wt% to 20 wt/wt%, 12 wt/wt% to 17 wt/wt%, 13 wt/wt% to 16 wt/wt%, 13 wt/wt% to 15 wt/wt%, 14 wt/wt% to 15 wt/wt%, or 13 wt/wt% to 14 wt/wt% emulsifier. In other embodiments, the composition comprises about 13 wt/wt%, 13.5 wt/wt%, 14 wt/wt%, 14.5 wt/wt%, 15 wt/wt%, 16 wt/wt%, 17 wt/wt%, 18 wt/wt%, 19 wt/wt% or 20 wt/wt% emulsifier. In still other embodiments, the emulsifier is a lecithin. In other embodiments, the lecithin is an egg yolk lecithin.

[0024] In some embodiments, the composition comprises about 0.05 wt/wt% to 1.5 wt/wt%, 0.1 wt/wt% to 1.0 wt/wt%, 0.2 wt/wt% to 0.8 wt/wt%, 0.3 wt/wt% to 0.7 wt/wt%, 0.4 wt/wt% to 0.6 wt/wt%, 0.4 wt/wt% to 0.5 wt/wt% oleate or salt thereof. In other embodiments, the composition comprises about 0.05 wt/wt%, 0.1 wt/wt%, 0.2 wt/wt%, 0.3 wt/wt%, 0.4 wt/wt%, 0.45 wt/wt%, 0.5 wt/wt%, 0.6 wt/wt%, 0.7 wt/wt%, 0.8 wt/wt%, 0.9 wt/wt%, 1.0 wt/wt% or 1.5 wt/wt% oleate or salt thereof. In still other embodiments, the oleate is sodium oleate. In still another embodiment, the oleate or sodium oleate is the pH modifier.

[0025] In some embodiments, the composition comprises about 20 wt/wt% to 50 wt/wt%, 30 wt/wt% to 50 wt/wt%, 35 wt/wt% to 45 wt/wt%, 30 wt/wt% to 45 wt/wt%, 37 wt/wt% to 42 wt/wt%, 38 wt/wt% to 40 wt/wt%, 30 wt/wt%, 31 wt/wt%, 32 wt/wt%, 33 wt/wt%, 34 wt/wt%, 35 wt/wt%,

36 wt/wt%, 37 wt/wt%, 38 wt/wt%, 39 wt/wt%, 40 wt/wt%, 41 wt/wt%, 42 wt/wt%, 43 wt/wt%, 44 wt/wt%, 45 wt/wt%, 46 wt/wt%, 47 wt/wt%, 48 wt/wt%, 49 wt/wt%, 50 wt/wt% of oil expressed as a percentage of the weight of the oil per the sum of weight of oil, emulsifier and oleate in a unit of the composition. In other embodiments, the oil is soybean oil.

[0026] In some embodiments, the composition comprises about 20 wt/wt% to 50 wt/wt%, 30 wt/wt% to 50 wt/wt%, 35 wt/wt% to 45 wt/wt%, 30 wt/wt% to 45 wt/wt%, 37 wt/wt% to 42 wt/wt%, 38 wt/wt% to 40 wt/wt%, 30 wt/wt%, 31 wt/wt%, 32 wt/wt%, 33 wt/wt%, 34 wt/wt%, 35 wt/wt%, 36 wt/wt%, 37 wt/wt%, 38 wt/wt%, 39 wt/wt%, 40 wt/wt%, 41 wt/wt%, 42 wt/wt%, 43 wt/wt%, 44 wt/wt%, 45 wt/wt%, 46 wt/wt%, 47 wt/wt%, 48 wt/wt%, 49 wt/wt%, 50 wt/wt% of oil expressed as a percentage of the weight of the oil per the sum of weight of oil and emulsifier in a unit of the composition. In other embodiments, the oil is soybean oil.

[0027] In some embodiments, the composition comprises about 40 wt/wt% to 80 wt/wt%, 50 wt/wt% to 70 wt/wt%, 55 wt/wt% to 65 wt/wt%, 57 wt/wt% to 63 wt/wt%, 58 to 60 wt/wt%, 35 wt/wt% to 40 wt/wt%, 30 wt/wt% to 40 wt/wt%, 50 wt/wt%, 51 wt/wt%, 52 wt/wt%, 53 wt/wt%, 54 wt/wt%, 55 wt/wt%, 56 wt/wt%, 57 wt/wt%, 58 wt/wt%, 59 wt/wt%, 60 wt/wt%, 61 wt/wt%, 62 wt/wt%, 63 wt/wt%, 64 wt/wt%, 65 wt/wt%, 66 wt/wt%, 67 wt/wt%, 68 wt/wt%, 69 wt/wt%, 70 wt/wt% of emulsifier expressed as a percentage of the weight of emulsifier per the sum of weight of oil, emulsifier and oleate in a unit of the composition. In other embodiments, the emulsifier is a lecithin. In still other embodiments, the lecithin is an egg yolk lecithin.

[0028] In some embodiments, the composition comprises about 40 wt/wt% to 80 wt/wt%, 50 wt/wt% to 70 wt/wt%, 55 wt/wt% to 65 wt/wt%, 57 wt/wt% to 63 wt/wt%, 58 to 60 wt/wt%, 35 wt/wt% to 40 wt/wt%, 30 wt/wt% to 40 wt/wt%, 50 wt/wt%, 51 wt/wt%, 52 wt/wt%, 53 wt/wt%, 54 wt/wt%, 55 wt/wt%, 56 wt/wt%, 57 wt/wt%, 58 wt/wt%, 59 wt/wt%, 60 wt/wt%, 61 wt/wt%, 62 wt/wt%, 63 wt/wt%, 64 wt/wt%, 65 wt/wt%, 66 wt/wt%, 67 wt/wt%, 68 wt/wt%, 69 wt/wt%, 70 wt/wt% of emulsifier expressed as a percentage of the weight of emulsifier per the sum of weight of oil and emulsifier in a unit of the composition. In other embodiments, the emulsifier is a lecithin. In still other embodiments, the lecithin is an egg yolk lecithin.

[0029] In some embodiments, the ratio of oil to NK-1 receptor antagonist (wt%:wt%) in the composition ranges from about 5:1 to 20:1, 5:1 to 15:1, 5:1 to 10:1, 11:1 to 20:1, 11:1 to 15:1, 12:1 to 16:1, 12:1 to 14:1, 11:1 to 15:1, 12:1 to 14:1, 12.5:1 to 13.5:1, 13:1 to 14:1, or 12:1 to 15:1. In other embodiments, the ratio of oil to NK-1 receptor antagonist (wt%:wt%) in the composition is

about 11:1 to 20:1, 11:1 to 15:1, 12:1 to 16:1, 12:1 to 14:1, 5:1, 6:1, 7:1, 8:1, 9:1, 10:1, 11:1, 11.5:1, 12:1, 12.5:1, 13:1, 13.5:1, 14:1, 14.5:1 or 15:1, 15.5:1, 16:1.

[0030] In some embodiments, the ratio of emulsifier to NK-1 receptor antagonist (wt%:wt%) in the composition ranges from about 10:1 to 30:1, 10:1 to 20:1, 15:1 to 30:1, 20:1 to 25:1, 18:1 to 22:1, 19:1 to 20:1, or 10:1 to 30:1. In other embodiments, the ratio of emulsifier:NK-1 receptor antagonist (wt%:wt%) in the composition is about 10:1, 11:1, 13:1, 14:1, 15:1, 18:1, 19:1, 20:1, 21:1, 22:1 23:1, 24:1, 25:1, or 30:1.

[0031] In some embodiments, the ratio of (emulsifier plus oil) to NK-1 receptor antagonist (wt%:wt%) in the composition ranges from about 20:1 to 40:1, 25:1 to 35:1, 30:1 to 35:1, or 32:1 to 34:1. In other embodiments, the ratio of (emulsifier plus oil) to NK-1 receptor antagonist is about 25:1, 26:1, 27:1, 28:1, 29:1 30:1, 31:1, 32:1, 33:1, 34:1, 35:1, 36:1, 37:1, 38:1 or 40:1.

[0032] In some embodiments, the ratio of emulsifier to oil (wt%:wt%) in the composition ranges from about 0.5:1, to 4:1, 1:1 to 2:1, 1.25:1 to 1.75:1, or 1.4:1 to 1.6:1. In other embodiments, the ratio of emulsifier to oil (wt%:wt%) in the composition is about 0.5:1, 0.5:1, 0.6:1, 0.7:1, 0.8:1, 0.9:1, 1:1, 1.1:1, 1.2:1, 1.3:1, 1.4:1, 1.5:1, 1.6:1, 1.7:1, 1.8:1, 1.9:1, 2:1, 1.05:1, 1.15:1, 1.25:1, 1.35:1, 1.45:1, 1.55:1, 1.65:1, 1.75:1, 1.85:1, or 1.95:1.

[0033] In some embodiments, a therapeutic dose of the pharmaceutical composition comprises about 1 to 4 g, 1.5 to 3 g, 1.8 to 2.8 g, 2.3 to 2.8 g, 1.8 to 2.3 g, 1 g, 1.1 g, 1.2 g, 1.3 g, 1.4 g, 1.5 g, 1.6 g, 1.7 g, 1.8 g. 1.9 g, 2 g, 2.1 g, 2.2 g, 2.3 g, 2.4 g, 2.5 g, 2.6 g, 2.7 g, 2.8 g. 2.9 g, 3 g, 3.1 g, 3.2 g, 3.3 g, 3.4 g, 3.5 g, 3.6 g, 3.7 g, 3.8 g. 3.9 g, 4 g emulsifier. In other embodiments, the emulsifier is a lecithin. In still other embodiments, the emulsifier is egg yolk lecithin.

[0034] In some embodiments, a therapeutic dose of the pharmaceutical composition comprises about 0.5 to 3 g, 1 to 2.5 g, 1 to 2 g, 1 to 1.5 g, 1.5 g to 2 g, 0.5g 0.6 g, 0.7 g, 0.8 g, 0.9 g, 1 g, 1.1 g, 1.2 g, 1.3 g, 1.4 g, 1.5 g, 1.6 g, 1.7 g, 1.8 g. 1.9 g, 2 g, 2.1 g, 2.2 g, 2.3 g, 2.4 g, 2.5 g oil. In other embodiments, the oil is soybean oil.

[0035] In some embodiments, a therapeutic dose of the pharmaceutical composition comprises about 50 to 600 mg, 100 to 600 mg, 100 to 500 mg, 100 to 400 mg, 100 to 300 mg, 100 to 200 mg, 200 to 400 mg, 50 to 250 mg, 75 to 200 mg, 100 to 150 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 160 mg, 170 mg, 180 mg, 190 mg, 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, or 600 mg of the NK-1 receptor antagonist.

[0036] In some embodiments, the composition comprises about 0 wt/wt% to 10 wt/wt%, 1 wt/wt% to 9 wt/wt%, 2 wt/wt% to 6 wt/wt%, 2 wt/wt% to 4 wt/wt% or 2 wt/wt% to 3 wt/wt% co-surfactant.

In other embodiments, the composition comprises less than 10 wt/wt%, less than 9 wt/wt%, less than 8 wt/wt%, less than 7, less than 6 wt/wt%, less than 5 wt/wt%, less than 4 wt/wt%, less than 3 wt/wt%, less than 2 wt/wt% or less than 1 wt/wt% co-surfactant.

[0037] In some embodiments, the composition comprises about 0 wt/wt% to 10 wt/wt%, 1 wt/wt% to 9 wt/wt%, or 2 wt/wt% to 6 wt/wt% ethanol. In other embodiments, the composition comprises less than 10 wt/wt%, less than 9 wt/wt%, less than 8 wt/wt%, less than 7, less than 6 wt/wt%, less than 5 wt/wt%, less than 4 wt/wt%, less than 3 wt/wt%, less than 2 wt/wt% or less than 1 wt/wt% ethanol.

[0038] In some embodiments, the aqueous phase of the emulsion comprises a tonicity agent, a pH modifier, and water.

[0039] In some embodiments, the aqueous phase of the emulsion comprises an osmotic agent, a pH modifier, and water.

[0040] In some embodiments, the aqueous phase of the emulsion comprises a tonicity agent, an osmotic agent, a pH modifier, and water.

[0041] In some embodiments, the aqueous phase further comprises a buffer.

[0042] In some embodiments, the aqueous phase comprises a buffer but does not comprise a pH modifier which is different from the buffer. In other embodiments, the buffer functions as both a pH modifier agent and a buffer.

[0043] In some embodiments, when the aqueous phase comprises a buffer, the composition contains no tonicity agent.

[0044] In some embodiments, the buffer is selected from the group consisting of phosphate buffer, citrate buffer, Tris buffer, carbonate buffer, succinate buffer, maleate buffer and borate buffer. In other embodiments, the buffer is selected from the group, phosphate buffered saline (PBS), modified PBS (PBS-mod) and citrate buffer.

[0045] In some embodiments, the aqueous phase comprises a buffer, that when mixed with the oil phase will provide a substantially isotonic oil in water emulsion.

[0046] In some embodiments, the osmotic agent is selected from the group consisting of glycerol, sorbitol, xylitol, mannitol, glucose, trehalose, maltose, sucrose, raffinose, lactose, dextran, polyethylene glycol, or propylene glycol. In other embodiments, the osmotic agent is an inorganic salt such as sodium chloride and mixtures thereof.

[0047] In some embodiments, the composition has a pH of about 6 to 9, 7 to 9, 7.5 to 9, 7.5 to 8.5, 8 to 9, 6 to 8, 7 to 8, or 6, 7, 8 or 9.

[0048] In some embodiments, the composition comprises about 0 wt/wt% to 25 wt/wt%, 2 wt/wt% to 20 wt/wt%, 3 wt/wt% to 15 wt/wt%, or 3 wt/wt% to 8 wt/wt% tonicity agent. In other embodiments, the composition comprises about 1 wt/wt%, 2 wt/wt%, 3 wt/wt%, 4 wt/wt%, 5 wt/wt%, 6 wt/wt%, 7 wt/wt%, 8 wt/wt%, 9 wt/wt%, or 10 wt/wt%, 11 wt/wt%, 12 wt/wt%, 13 wt/wt%, 14 wt/wt%, 15 wt/wt%, 16 wt/wt%, 17 wt/wt%, 18 wt/wt%, 19 wt/wt%, or 20 wt/wt%, 21 wt/wt%, 22 wt/wt%, 23 wt/wt%, 24 wt/wt%, 25 wt/wt% tonicity agent. In still other embodiments, the composition comprises no tonicity agent.

[0049] In some embodiments, the composition comprises about 0 wt/wt% to 25 wt/wt%, 2 wt/wt% to 20 wt/wt%, 3 wt/wt% to 15 wt/wt%, or 3 wt/wt% to 8 wt/wt% osmotic agent. In other embodiments, the composition comprises about 1 wt/wt%, 2 wt/wt%, 3 wt/wt%, 4 wt/wt%, 5 wt/wt%, 6 wt/wt%, 7 wt/wt%, 8 wt/wt%, 9 wt/wt%, or 10 wt/wt%, 11 wt/wt%, 12 wt/wt%, 13 wt/wt%, 14 wt/wt%, 15 wt/wt%, 16 wt/wt%, 17 wt/wt%, 18 wt/wt%, 19 wt/wt%, or 20 wt/wt%, 21 wt/wt%, 22 wt/wt%, 23 wt/wt%, 24 wt/wt%, 25 wt/wt% osmotic agent. In still other embodiments, the composition comprises no osmotic agent.

[0050] In some embodiments, the aqueous phase comprises a dose of dexamethasone sodium phosphate in a therapeutic dose of the pharmaceutical composition. In other embodiments, the dose of dexamethasone sodium phosphate ranges from about 0.5 mg to 30 mg, 0.5 mg to 25 mg, 1 mg to 20 mg, 10 mg to 20 mg, or 3 mg to 16 mg. In still other embodiments, the dose of dexamethasone sodium phosphate is about 9 mg or 16 mg in a therapeutic dose of the pharmaceutical composition. In these embodiments comprising a dose of dexamethasone, the therapeutic dose of the pharmaceutical composition comprises about 50 to 600 mg, 100 to 600 mg, 100 to 500 mg, 100 to 400 mg, 100 to 300 mg, 100 to 200 mg, 200 to 400 mg, 50 to 250 mg, 75 to 200 mg, 100 to 150 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 160 mg, 170 mg, 180 mg, 190 mg, 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, or 600 mg of the NK-1 receptor antagonist.

[0051] In some embodiments, the oil phase comprises a dose of dexamethasone in a therapeutic dose of the pharmaceutical composition. In other embodiments, the dose of dexamethasone ranges from about 0.5 mg to 30 mg, 0.5 mg to 20 mg, 1 mg to 18 mg, 10 mg to 20 mg, or 3 mg to 16 mg. In other embodiments, the dose of dexamethasone is about 8 mg or 12 mg in a therapeutic dose of the pharmaceutical composition. In these embodiments comprising a dose of dexamethasone, the therapeutic dose of the pharmaceutical composition comprises about 50 to 600 mg, 100 to 600 mg, 100 to 500 mg, 100 to 400 mg, 100 to 300 mg, 100 to 200 mg, 200 to 400 mg, 50 to 250 mg, 75 to 200 mg, 100 to 150 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 160 mg, 170 mg, 180

mg, 190 mg, 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, or 600 mg of the NK-1 receptor antagonist

[0052] In some embodiments, the emulsion comprises about 0.002 wt/wt% to 0.2 wt/wt%, 0.003 wt/wt% to 0.16 wt/wt%, 0.02 wt/wt% to 0.1 wt/wt% dexamethasone sodium phosphate.

[0053] In some embodiments, the composition is a stable system maintaining an intensity-weighted mean particle size as determined by dynamic light scattering (DLS) of about 50 nm to 1000 nm, 50 to 500 nm, 50 nm to 400 nm, 50 nm to 300 nm, 50 nm to 200 nm or 50 nm to 100 nm. In another embodiment, the average droplet size is maintained below 500 nm for a period of at least 1 month, 3 months, 6 months, 9 months, 12 months, 2 years or 3 years at room temperature. In other embodiments, the average droplet size is maintained below 500 nm for a period of at least 1 month, 3 months, 6 months, 9 months, 12 months, 2 years or 3 years at 5 °C.

[0054] In another aspect, a method for preparing an emulsion comprising an NK-1 receptor antagonist compound and suitable for parenteral administration is provided.

[0055] In some embodiments, the administration is intravenous administration.

[0056] In some embodiments, the method comprises: a) preparing an oil phase by dissolving the antagonist compound and an emulsifier in ethanol, then adding in oil to generate an oil-based mixture; b) preparing an aqueous phase by mixing water, optionally with a tonicity agent, optionally with an osmotic agent and optionally with a pH modifier and optionally with a buffer to generate an aqueous mixture; c) combining the oil-based mixture and the aqueous mixture and subjecting this to high speed homogenization to generate a crude emulsion; and d) subjecting the crude emulsion to high pressure homogenization to generate a fine emulsion.

[0057] In some embodiments, preparing the oil phase further comprises dissolving dexamethasone with the antagonist compound and the emulsifier in the ethanol.

[0058] In some embodiments, the method comprises: a) combining a NK-1 receptor antagonist, an emulsifier, and an alcohol with an oil to generate an oil phase; (b) combining water, a tonicity agent, a pH modifier, and optionally a buffer to generate an aqueous phase; (c) homogenizing the oil phase with the aqueous phase to generate the pharmaceutical emulsion; and (d) sterilizing the pharmaceutical emulsion. In other embodiments, the homogenizing comprises high speed homogenization.

[0059] In some embodiments, the method comprises: a) preparing an oil phase by dissolving the antagonist compound and an emulsifier in ethanol and oil to generate an oil-based mixture; b) preparing an aqueous phase by mixing water, optionally with a tonicity agent, optionally with an

osmotic agent and optionally with a pH modifier and optionally with a buffer to generate an aqueous mixture; c) combining the oil-based mixture and the aqueous mixture and subjecting this to homogenization to generate a crude emulsion; and d) subjecting the crude emulsion to homogenization to generate a fine emulsion. In other embodiments, the subjecting the homogenization to generate a crude emulsion is high-speed homogenization. In still other embodiments, the homogenization to generate a fine emulsion is a high pressure homogenization.

[0060] In some embodiments, preparing the oil phase further comprises dissolving dexamethasone with the antagonist compound and the emulsifier in the ethanol and oil.

[0061] In some embodiments, preparing the aqueous phase further comprises mixing dexamethasone with the water, tonicity agent, pH modifier, and a buffer. In other embodiments, the dexamethasone is a salt of dexamethasone. In still other embodiments, the dexamethasone is dexamethasone sodium phosphate.

[0062] In some embodiments, the method further comprises sterilizing the fine emulsion to generate the final emulsion, wherein the final emulsion is suitable for injection into a subject.

[0063] In some embodiments, the dissolution in ethanol is performed at a temperature of about 25 °C to 80 °C, 40 °C to 75 °C, 60 °C to 70 °C, or at about 25 °C, 35 °C, 45 °C, 60 °C, 65 °C, 70 °C or 75 °C.

[0064] In some embodiments, the high-speed homogenization is performed at a speed of about 2,000 rpm (revolutions per minute) to 25,000 rpm. In other embodiments, the high-speed homogenization is performed at a speed of about 20,000 rpm. In still other embodiments, the high-speed homogenization is performed at a speed of about 3600 rpm.

[0065] In some embodiments, the high-speed homogenization is performed for a time period of about 0.5 min to 1 hour, 1 min to 45 min, or 1 min to 30 min. In other embodiments, the high-speed homogenization is performed for a time period of about 20 to 40 min or for about 30 min.

[0066] In some embodiments, the high-speed homogenization is performed at about 10 °C to about 60 °C, 20 °C to about 60 °C, about 30 °C to about 50 °C, or about 35 °C to about 45 °C. In another embodiment, the high-speed homogenization is performed at about 25 °C, 30 °C, 35 °C, 40 °C, 45 °C or 50 °C.

[0067] In some embodiments, the high-pressure homogenization is performed at a pressure of about 10,000 psi (pounds per square inch) to 30,000 psi. In other embodiments, the high-pressure homogenization is performed at a pressure of about 20,000 psi.

[0068] In some embodiments, the high-pressure homogenization is performed with cooling. In another embodiment, the high-pressure homogenization is performed with cooling which is sufficient to bring the temperature of the emulsion at the outlet of the process to about 0 °C to about 60 °C, about 10 °C to about 40 °C, about 20 °C to about 30 °C, or to about 20 °C, 25 °C or 30 °C within the time period.

[0069] In some embodiments, the sterilizing the fine emulsion comprises filtering the fine emulsion through a nylon filter. In other embodiments, the nylon filter is a Posidyne® filter. In yet another embodiment, the filter has a pore size of about 0.2 μm (micrometers).

[0070] In another aspect, the compositions described herein are for treatment of a subject, and the composition is administered via injection to a subject in need.

[0071] In some embodiments, the compositions are for use in a method for the treatment of emesis induced by a chemotherapeutic agent, by radiation-induced nausea and vomiting, and/or by post-operative induced nausea and vomiting in a subject. In other embodiments, the treatment comprises administering to the subject a composition comprising an NK-1 receptor antagonist as described herein. In still other embodiments, the compositions are for use in preventing or treating acute and delayed nausea and vomiting.

[0072] Additional embodiments of the present compositions and methods and the like, will be apparent from the following description, drawings, examples, and claims. As can be appreciated from the foregoing and following description, each and every feature described herein, and each and every combination of two or more of such features, is included within the scope of the present disclosure provided that the features included in such a combination are not mutually inconsistent. In addition, any feature or combination of features may be specifically excluded from any embodiment of the present invention. Additional aspects and advantages of the present invention are set forth in the following description and claims, particularly when considered in conjunction with the accompanying examples and drawings.

BRIEF DESCRIPTION OF DRAWINGS

[0073] FIGS. 1A-1D provides microscope images of samples from Examples 1, 2, 3 and 6 after a freeze-thaw cycle. FIG. 1A: Example 1, FIG. 1B: Example 2, FIG. 1C: Example 3, FIG. 1D: Example 6

[0074] FIG. 2 shows plasma levels of aprepitant after injection of a fosaprepitant solution (●) or an aprepitant emulsion prepared as described herein (▲).

[0075] FIG. 3 shows plasma levels of aprepitant after injection of a solution of fosaprepitant (▲) or after injection of an emulsion containing aprepitant and dexamethasone prepared as described herein (●).

[0076] FIG. 4 shows plasma levels of dexamethasone after injection of a solution of dexamethasone sodium phosphate (●) or after injection of an emulsion containing aprepitant and dexamethasone prepared as described herein (▲).

DETAILED DESCRIPTION

[0077] Various aspects now will be described more fully hereinafter. Such aspects may, however, be embodied in many different forms and should not be construed as limited to the embodiments set forth herein; rather, these embodiments are provided so that this disclosure will be thorough and complete, and will fully convey its scope to those skilled in the art.

I. DEFINITIONS

[0078] As used in this specification, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to a "polymer" includes a single polymer as well as two or more of the same or different polymers, reference to an "excipient" includes a single excipient as well as two or more of the same or different excipients, and the like.

[0079] Where a range of values is provided, it is intended that each intervening value between the upper and lower limit of that range and any other stated or intervening value in that stated range is encompassed within the disclosure. For example, if a range of 1 μm to 8 μm is stated, it is intended that 2 μm, 3 μm, 4 μm, 5 μm, 6 μm, and 7 μm are also explicitly disclosed, as well as the range of values greater than or equal to 1 μm and the range of values less than or equal to 8 μm. As used herein, the term “about” means ±5%, ±10%, or ±20% of the value being modified.

[0080] The term “emulsion” or “emulsion formulation” means a colloidal dispersion of two immiscible liquids in the form of droplets, whose diameter, in general, is between 10 nanometers and 100 microns. An emulsion is denoted by the symbol O/W (oil-in-water) if the continuous phase is an aqueous solution and by W/O (water-in-oil) if the continuous phase is an oil. Other examples of emulsions such as O/W/O (oil-in-water-oil) include oil droplets contained within aqueous droplets dispersed in a continuous oil phase.

[0081] “Physically stable” emulsions will meet the criteria under USP <729>, which defines universal limits for (1) mean droplet size not exceeding 500 nm or 0.5 μm and (2) the population of large-diameter fat globules, expressed as the volume-weighted percentage of fat greater than 5 μm

(PFAT5) not exceeding 0.05%, at 5 ºC or room temperature for a designated storage time period. In addition, physically stable emulsions will have no visible NK-1 receptor antagonist crystals upon storage at 5 °C or room temperature for a designated time period. Crystals are considered visible when viewed at magnification of 4X to 10X. An emulsion is physically stable if it meets the criteria under USP <729> and NK-1 receptor antagonist crystals are not visible upon storage at 5 °C or room temperature for a time period equal to or at least 1 week, 2 weeks, 4 weeks, 1 month, 2 months, 6 months, 1 year or 2 years.

[0082] "Chemically stable" emulsions of the disclosure are ones in which the concentration of the active component (i.e., the drug being delivered) does not change by more than about 20% under appropriate storage conditions for at least 1 month. In certain embodiments, the concentration the NK-1 receptor antagonist in an emulsion of the present disclosure does not change by more than about 5%, 10%, 15% or 20% under appropriate storage conditions for at least 1, 2, 3, 4, 5, 6, 9, 12, 15, 18, or 24 months.

[0083] In one example, the stable emulsion compositions of the disclosure are stable over a wide range of temperatures, e.g., −20 °C to 40 °C. The compositions of the disclosure may be stored at about 5 °C to about 25 °C.

[0084] "Oil phase" in a water-in-oil emulsion refers to all components in the formulation that individually exceed their solubility limit in the water phase; these are materials that generally have solubilities of less than 1% in distilled water, however, water phase components such as salts may decrease the solubility of certain oils resulting in their partitioning into the oil phase. The oil phase refers to the non-aqueous portion of a water-in-oil emulsion.

[0085] "Aqueous phase" or "water phase" in a water-in-oil emulsion refers to the water present and any components that are water soluble, i.e., have not exceeded their solubility limit in water. "Aqueous phase", as used herein, includes a water-containing liquid which can contain pharmaceutically acceptable additives such as acidifying, alkalizing, buffering, chelating, complexing and solubilizing agents, antioxidants and antimicrobial preservatives, humectants, suspending and/or viscosity modifying agents, tonicity and wetting or other biocompatible materials. The aqueous phase refers to the non-oil portion of a water-in-oil emulsion.

[0086] An "emulsifier" refers to a compound that deters the separation of the injectable emulsion into individual oil and aqueous phases. Emulsifiers useful in the present disclosure generally are (1) compatible with the other ingredients of the stable emulsions of the present disclosure, (2) do not

interfere with the stability or efficacy of the drugs contained in the emulsions, (3) are stable and do not deteriorate in the preparation, and (4) are non-toxic.

[0087] Suitable emulsifiers include, but are not limited to, propylene glycol mono- and di-fatty acid esters, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene fatty acid esters, polyoxyethylene-polyoxypropylene co-polymers and block co-polymers, salts of fatty alcohol sulphates, sorbitan fatty acid esters, esters of polyethylene-glycol glycerol ethers, oil and wax based emulsifiers, glycerol monostearate, glycerine sorbitan fatty acid esters and phospholipids.

[0088] A "phospholipid" refers to a triester of glycerol in which the secondary alcohol and one of the primary alcohols has been esterified with fatty acids and the other primary alcohol has been esterified with a phosphate group. Exemplary phospholipids useful in the present invention include, but are not limited to, phosphatidyl chlorine, lecithin (a mixture of choline ester of phosphorylated diacylglyceride), phosphatidylethanolamine, phosphatidylglycerol, phosphatidic acid with about 4 to about 22 carbon atoms, and more generally from about 10 to about 18 carbon atoms and varying degrees of saturation. The phospholipids can have any combination of fatty acid as its fatty acyl side chain, for example, the phospholipids can have a saturated fatty acid such as a decanoic acid, lauric acid, myristic acid, palmitic acid, stearic acid, icosanoic acid, (a C20 saturated fatty acid); sodium behenic acid, or an unsaturated fatty acid such as myristoleic acid, palmitoleic acid, oleic acid, sodium linoleic acid, alpha linolenic acid, sodium arachidonic acid, eicosapentanoic acid, and the like. The two fatty acyl residues on the phospholipids may be the same or they may be different fatty acids. The phospholipid component of the drug delivery composition can be either a single phospholipid or a mixture of several phospholipids. The phospholipids should be acceptable for the chosen route of administration.

[0089] In one aspect, the phospholipids used as emulsifiers in the present invention are naturally occurring phospholipids from a natural origin. For example, naturally occurring lecithin is a mixture of the diglycerides of stearic, palmitic, and oleic acids, linked to the choline ester of phosphoric acid, commonly called phosphatidylcholine, and can be obtained from a variety of sources such as eggs and soya beans. Soy lecithin and egg lecithin (including hydrogenated versions of these compounds) have been characterized in various compositions and are generally recognized to be safe, have combined emulsification and solubilization properties, and tend to be broken down into innocuous substances more rapidly than most synthetic surfactants.

[0090] The term "lecithin" includes a complex mixture of acetone-insoluble phosphatides, of which phosphatidylcholine is a significant component. The term lecithin is also used as a synonym for

phosphatidylcholine. Useful lecithins include, but are not limited to, egg yolk-, egg-, soybean-, and corn-derived lecithin. In one embodiment, the emulsifier is lecithin, such as egg yolk-derived lecithin. The terms egg lecithin and egg yolk derived lecithin are used interchangeably throughout. The compositions described herein preferably comprise lecithin as an emulsifier.

[0091] The amount of phospholipids, by weight, in the emulsions of the present disclosure may be within a range of about 10 wt/wt% to about 20 wt/wt%, 11 wt/wt% to 19 wt/wt%, 11 wt/wt% to 15 wt/wt%, 12 wt/wt% to 13 wt/wt%, 13 wt/wt% to 14 wt/wt%, 13 wt/wt% to 20 wt/wt%, or 12 wt/wt% to 18 wt/wt%. In certain embodiments, the phospholipids in the emulsions are at a concentration, by weight, about 11 wt/wt%, 12 wt/wt%, 12.5 wt/wt%, 13 wt/wt%, 13.5 wt/wt%, 14 wt/wt%, 14.5 wt/wt%, or 15 wt/wt%.

[0092] "Oil" refers to an organic liquid of mineral, vegetable, animal, essential or synthetic origin, including, for example, aliphatic or wax-based hydrocarbons, aromatic hydrocarbons or mixed aliphatic and aromatic hydrocarbons.

[0093] The term "buffer" or "buffered" as used herein means a solution containing both a weak acid and its conjugate base, whose pH changes only slightly upon addition of acid or base. As used herein, the phrase "buffering agent" means a species whose inclusion in a solution provides a buffered solution. Buffers are well-known in the art and readily available. Buffers for use according to the methods and compositions described herein include but are not limited to phosphate, citrate, Tris, carbonate, succinate, maleate, borate, MES, Bis-Tris, ADA, aces,PIPES, MOPSO, Bis-Tri Propane, BES, MOPS, TES, HEPES, DIPSO, MOBS, TAPSO, Trizma, HEPPSO, POPSO, TEA, EPPS, Tricine, Gly-Gly, Bicine, GEPBS, TAPS, AMPD, TABS, AMPSO, CHES, CAPSO, AMP, CAPS, and CABS.

[0094] The term "therapeutic agent" describes any natural or synthetic compound which has a biological activity. A "therapeutically effective amount" means the amount that, when administered to an animal or subject for treating or preventing a disorder, condition, or disease, is sufficient to effect treatment for that disorder, condition, or disease.

[0095] As used herein, the term "emesis" includes nausea and vomiting.

[0096] The term "substantially" in reference to a certain feature or entity means to a significant degree or nearly completely (i.e. to a degree of 85% or greater) in reference to the feature or entity.

II. NK-1 RECEPTION ANTAGONIST EMULSION AND METHODS OF MAKING

[0097] The present disclosure is directed to stable pharmaceutical compositions including an NK-1 receptor antagonist, a surfactant or mixtures of surfactants, a co-surfactant, an oil, with an aqueous

phase. The composition can be an injectable emulsion and is in the form of an oil-in-water emulsion which remains stable over an extended period of time and which is suitable for dilution and intravenous administration.

[0098] The NK-1 receptor antagonist compound is present in the oil phase with an emulsifier, a co-surfactant and an oil. The oil phase is then combined with an aqueous phase comprising water and a tonicity agent as described below to generate the stable emulsion. Prior to combining the oil phase with the aqueous phase, the oil phase will have an oil:antagonist compound ratio of about 11:1 to 30:1, 11:1 to 15:1, or about 13:11. For example, in formulating an oil phase comprising aprepitant, use of an oil:aprepitant ratio of about 13:1 was surprisingly found to produce, when mixed with the water phase, an emulsion which is more stable as compared to an emulsion in which the oil phase contains an oil:aprepitant ratio of less than about 12:1 or 11:1, and/or greater than about 15:1, 20:1, or 30:1. Accordingly, in some embodiments the stable emulsion comprising an NK-1 receptor antagonist and to be administered to the subject can have an oil:antagonist compound ratio of about 11:1 to 30:, 11:1 to 15:1, or about 13:11. Also contemplated, however, are emulsions in which the oil:antagonist compound ratio is about 5:1 to 20:1, 5:1 to 15:1 or 5:1 to 10:1.

[0099] Moreover, the present compositions also possess favorable stability properties when the amount of emulsifier in the oil phase is greater than the amount of oil. For example, the oil phase contains an emulsifier:oil ratio of about 5:1 to 1:1, 3:1 to 1:1 or a ratio of about 1.5:1. Such ratios of emulsifier:oil have surprisingly been found to impart greater stability on a final emulsion which is suitable for injection into a patient. For example, an aprepitant emulsion having a phospholipid:oil ratio within the oil phase of about 1.5:1 was found to have greater stability than a similar aprepitant emulsion, wherein the oil phase comprises a phospholipid:oil ratio of about 0.01:1, 0.1:1, 0.5:1 or 0.9:1.

[0100] Suitable NK-1 receptor antagonists for use in the presently described pharmaceutical emulsions include RP 67580 ((3aR,7aR)-Octahydro-2-[1-imino-2-(2-methoxyphenyl)ethyl]-7,7-diphenyl-4H-isoindol)), WIN 51078 (17-β-Hydroxy-17-α-ethynyl-5-α-androstano[3,2-b]pyrimido[1,2-a]benzimidazole), l-733,060, (((2S,3S)-3-[[3,5-bis(Trifluoromethyl) phenyl]methoxy]-2-phenylpiperidine hydrochloride), l-703,606 (cis-2-(Diphenylmethel)-N- ([2-iodophenyl]methyl)-1-azabicyclo(2.2.2)octan-3-amine) MDL 105,212 (R)-1-[2-[3-(3,4-dichlorophenyl)-1-(3,4,5-trimethoxybenzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenylpiperidine-4-carboxamide hydrochloride), serlopitant, maropitant, Antagonist D, aprepitant, fosaprepitant, R116301, CGP49823, CP-96345, CP-99994, GR-203040, MDL-103392, l-760735, SDZ-NKT-343,

nolpitanitium (SR-140333), AV608, rolapitant, SCH 900978, AV608, GSK424887 (GlaxoSmithKline), GSK206136 (GlaxoSmithKline), GR-205171, CP-99994, TAK 637 ((S)-7-(3,5-Bis-trifluoromethyl-benzyl)-9-methyl-5-p-tolyl-8,9,10,11-tetrahydro-7H-1,7,11a-triaza-cycloocta[b]naphthalene-6,12-dione), LY303870 ([(R)-1-[N-(2-methoxybenzyl)acetylamino]-3-(1H-indol-3-yl)-2-[N-(2-(4- (piperidin-1-yl)piperidin-1-yl)acetyl)amino]propane]), LY686017 ((2-chloro-phenyl)-{2-[5-pyridin-4-yl-1-(3,5-bistrifluoromethyl-benzyl)-1H-[1,2,3]triazol-4-yl]-pyridin-3-yl}-methanone), E-6006, casopitant/GW679769 ((2R,4S)-4-(4-acetylpiperazin-1-yl)-N-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl)ethyl]-2-(4-fluoro-2-methylphenyl)-N-methylpiperidine-1-carboxamide), vestipitant, orvepitant and orvepitant maleate, befetupitant, netupitant, ezlopitant, CP-122721, MPC-4505 (Myriad Genetics, Inc.), CP-122721 (Pfizer, Inc.), CJ-1 2,255 (Pfizer, Inc.), SRR 240600 (Sanofi-Aventis), or TA-5538 (Tanabe Seiyaku Co.) including all pharmaceutically acceptable salts thereof.

1. Oil Phase

[0101] The oil (hydrophobic) phase comprises an oil. Triglycerides are exemplary oils for use in the compositions described herein. In certain embodiments the oil is or comprises a vegetable oil. "Vegetable oil" refers to oil derived from plant seeds or nuts. Vegetable oils are typically "long-chain triglycerides" (LCTs), formed when three fatty acids (usually 14 to 22 carbons in length, with unsaturated bonds in varying numbers and locations, depending on the source of the oil) form ester bonds with the three hydroxyl groups on glycerol. In certain embodiments, vegetable oils of highly purified grade (also called "super refined") are used to ensure safety and stability of the oil-in-water emulsions. In certain embodiments hydrogenated vegetable oils, which are produced by controlled hydrogenation of the vegetable oil, may be used. Exemplary vegetable oils include but are not limited to almond oil, babassu oil, black currant seed oil, borage oil, canola oil, castor oil, coconut oil, corn oil, cottonseed oil, olive oil, peanut oil, palm oil, palm kernel oil, rapeseed oil, safflower oil, soybean oil, sunflower oil and sesame oil. Hydrogenated and/or or partially hydrogenated forms of these oils may also be used. In specific embodiments, the oil is or comprises safflower oil, sesame oil, corn oil, olive oil and/or soybean oil. In more specific embodiments, the oil is or comprises safflower oil, and/or soybean oil. The oil is present in the emulsion at about 9 wt/wt%, though this may vary between about 5 wt/wt% to 12 wt/wt% or 9 wt/wt% to 10 wt/wt%.

[0102] To generate the oil phase, the NK-1 receptor antagonist is first mixed with an emulsifier such as a phospholipid emulsifier. Examples 1-6 and 11-19 are examples in which NK-1 receptor antagonist emulsions made using an egg lecithin. A phospholipid emulsifier is added to a

concentration of greater than 10 wt/wt%, 11 wt/wt%, 12 wt/wt% or 13 wt/wt% of the emulsion but less than 15 wt/wt%, 17 wt/wt% or 20 wt/wt% of the emulsion.

[0103] The mixture of antagonist and emulsifier is dissolved in a co-surfactant such as a short chain alcohol (1 to 6 carbons). Examples 1-6 and 11-19 below are some examples in which the co-surfactant is ethanol. The mixture is mixed at an elevated temperature, such as at about 60 °C or 70 °C or at an elevated temperature within the range of about 50 °C or 70 °C, until the NK-1 receptor antagonist and emulsifier are dissolved. This mixture is then combined with the oil, such as soybean oil, by mixing again at an elevated temperature such as at about 60 °C to produce the oil phase containing the NK-1 receptor antagonist. Excess co-surfactant can be removed by standard evaporation methods including heating, or pressure reduction, or a combination thereof such employed in a rotary evaporator. In this process, about 10% to 100%, 20% to 95%, 80% to 100%, 90% to 100%, or 95% to 100% of the ethanol evaporates depending on preparation scale, any pressure reduction, and heating time.

[0104] In one embodiment, the NK-1 receptor antagonist and the emulsifier are dissolved in a co-surfactant and an oil. Examples 1-6 and 11-19 below are some examples in which the co-surfactant is ethanol and the oil is soybean oil, however, the methods can be used with any one or more of the co-surfactants and oils described herein. The mixture is mixed at an elevated temperature, such as at about 60 °C or 70 °C or at an elevated temperature within the range of about 50 °C or 70 °C, at least until the NK-1 receptor antagonist and emulsifier are dissolved to produce the oil phase containing the NK-1 receptor antagonist. The mixture of NK-1 receptor antagonist, emulsifier, co-surfactant and oil are mixed at the elevated temperature for about 15 min to 120 min, about 15 min to 45 min, about 30 min to 90 min, or for about 15 min, 30 min or 50 min.

[0105] Excess co-surfactant can be removed by standard evaporation methods including heating, or pressure reduction, or a combination thereof in a rotary evaporator. During this process, about 10% to 100%, 20% to 95%, 80% to 100%, 90% to 100%, or 95% to 100% of the ethanol evaporates depending on preparation scale, any pressure reduction, and heating time.

[0106] In one embodiment, dexamethasone is added to the oil phase comprising the NK-1 receptor antagonist, emulsifier and oil to generate an oil phase comprising both the NK-1 receptor antagonist and dexamethasone prior to mixing with the aqueous phase to generate the pharmaceutical emulsion for injection. Dexamethasone is added to the oil phase to provide a dose of about 12 mg dexamethasone.

2. Aqueous Phase

[0107] The aqueous phase of the NK-1 receptor antagonist emulsion can be a mixture of water and a tonicity agent, including those such as but not limited to sucrose, mannitol, glycerin or dextrose or a mixture thereof. Also included in the aqueous phase is a pH-modifying agent (pH modifier). Sodium oleate is used in Examples 1-3, 5, 6, and 11-15, and 17-19 below to adjust the pH of the emulsion to about 6 to 9, depending on the desired emulsion formulation. However, it is understood that the pH modifier can be other oleic acids or salts thereof including but not limited to sodium oleate, potassium oleate and ammonium oleate. The oleic acid can comprise about 0.1 wt/wt% to 1.0 wt/wt% or about 0.4 wt/wt% or 0.5 wt/wt% of the stable injectable emulsions as provided herein. The aqueous phase is produced by mixing water with the tonicity agent and pH modifier (e.g., sodium oleate). Additional pH modifiers that may be used include but are not limited to sodium hydroxide, potassium hydroxide, magnesium hydroxide, Tris, sodium carbonate and sodium linoleate. In some embodiments, the pH modifier comprises more than one pH modifier. For example, the aqueous phase may comprise both an oleate and a buffer such as a Tris buffer. The pH modifier used is effective for adjusting the pH of the emulsion to a preferred pH of about 6 to 9, 7 to 8, or about 6, 7, 8 or 9. The aqueous phase can readily form by mixing at room temperature.

[0108] The aqueous phase of the emulsion may further contain a buffering agent to promote stability of the emulsion formulation. The drug substance may degrade; for example, lipophilic drugs will partition into the oil phase, which will confer some degree of protection, but hydrolytic degradation may still occur at the oil-water interface. Possible chemical degradation within parenteral fat emulsions includes oxidation of unsaturated fatty acid residues present in triglyceride and lecithin, and hydrolysis of phospholipids leading to the formation of free fatty acids (FFA) and lysophospholipids. Such degradants lower pH, which may then promote further degradation. Thus, pH should be controlled during manufacture and emulsion formulations may include a buffering agent to provide additional control. Any decrease in pH over the assigned shelf-life may be indicative of chemical degradation. Suitable buffers are well known to the person skilled in the art and include but are not limited to a phosphate buffer, citrate buffer, Tris buffer, carbonate buffer, succinate buffer, maleate buffer or borate buffer. Tris buffer is used in Examples 11 and 19 below to adjust the pH of the emulsion to about 8 to 9. As shown in Examples 11 and 19, in some embodiments a buffer such as Tris buffer can be used in addition to another pH modifier (e.g., oleate or sodium oleate) to adjust or modify the pH of the emulsion. In some embodiments, the buffer is selected from the group, phosphate buffered saline (PBS), modified PBS (PBS-mod) and citrate buffer. In a particular

embodiment, the aqueous phase comprises a buffer, that when mixed with the oil phase will provide a substantially isotonic oil in water emulsion.

[0109] Buffering agents useful for the presently described compositions include, but are not limited to, a phosphate buffer, citrate buffer, Tris buffer, carbonate buffer, succinate buffer, maleate buffer or borate buffer. In a particular embodiment, the buffer is selected from the group, phosphate buffered saline (PBS), modified PBS (PBS-mod) and citrate buffer. In a particular embodiment, the aqueous phase comprises a buffer, that when mixed with the oil phase will provide a substantially isotonic oil in water emulsion. In some embodiments, when the aqueous phase contains a buffering agent, the aqueous phase does not include a tonicity agent. Also, when a buffer is added to the aqueous phase, a pH-adjusting agent may not be added to the aqueous phase. It is understood that a buffer can be added to the aqueous phase or the buffer can be added to the emulsion.

[0110] In some embodiments, the aqueous phase of the emulsion contains a tonicity agent such as sucrose. The tonicity agent is added to an aqueous phase having about 0% to 30%, 0% to 25% or about 20% of the tonicity agent (wt/wt). It was surprisingly found that a composition containing about 20% sucrose wt/wt in the aqueous phase produced an emulsion that was particularly stable as determined by freeze-thaw testing. Accordingly, preferred embodiments include an emulsion in which the aqueous phase comprises a tonicity agent which imparts greater chemical and/or physical stability as compared to an emulsion wherein the aqueous phase contains less than about 10%, 15% or 20% wt/wt tonicity agent or more than about 30%, 40% or 50% wt/wt tonicity agent.

[0111] In one embodiment, the aqueous phase further comprises dexamethasone sodium phosphate (also referred to as "dexamethasone phosphate"). Dexamethasone sodium phosphate is a corticosteroid which is freely soluble in water. Daily dosages for dexamethasone sodium phosphate range from about 0.5 mg to 20 mg, more preferably from about 14 mg to 18 mg or 16 mg, depending on the severity of the disease or disorder. Accordingly, an NK-1 receptor antagonist emulsion further comprising dexamethasone may contain dexamethasone sodium phosphate in the aqueous phase. Accordingly, the aqueous phase of an emulsion suitable for intravenous administration may contain about 0.5 mg to 20 mg, 14 mg to 18 mg or about 16 mg dexamethasone sodium phosphate.

[0112] In another embodiment, a solution of dexamethasone sodium phosphate can be mixed into the fine emulsion prior to sterile filtration to prepare an emulsion containing dexamethasone sodium phosphate in the aqueous phase,

3. Pharmaceutical Emulsion Formulations

[0113] The pharmaceutical compositions comprising NK-1 receptor antagonists as disclosed herein are sterile oil-in-water emulsions comprising the aqueous and oil phases described above. Also encompassed by the disclosure are methods for preparing stable emulsions comprising the receptor antagonist which are suitable for intravenous administration and which can be prepared according to the conventional manufacturing procedures using aseptic techniques.

[0114] The aqueous phase is combined with the oil phase, under high-speed homogenization to produce a coarse emulsion. Examples 1-6 and 12-19 provide examples of NK-1 receptor antagonist emulsions which are produced using compositions and methods disclosed herein. As described in these examples, the combined aqueous and oil phases is homogenized using an IKA Ultra-Turrax T25 dispersing instrument at a speed of 20,000 rpm for 1 min. The speed used in this first homogenization step may vary, for example, from 2000 rpm to 25,000 rpm, or from 15,000 rpm to 22,000 rpm. The time of the homogenization step can also vary, for example, from 0.5 min to 1 hour, or from 1 min to 45 min. This crude emulsion is then homogenized into a fine emulsion by a high-pressure homogenizer, which may be a microfluidizer. The interaction chamber and the cooling coil portions of the microfluidizer are cooled by water, such as by an ice bath. The temperature of the ice bath may be between 0 to 10 ºC, or 2 to 6 ºC. The temperature of the emulsion coming out of the high-pressure homogenization may be between 0 to 60 ºC, 15 ºC, to 60 ºC, 20 ºC to 40 ºC, or at about 25 ºC. The microfluidizer is first primed with water and then the crude emulsion is introduced. The output from the homogenizer is initially run to waste to remove priming water, and priming water and emulsion mixtures, and then collected in a clean vessel when the stream becomes consistent in appearance. The high-pressure homogenizer cycle may be repeated to sufficiently reduce oil droplet size. The pressure used for the homogenization may vary. The pressures may be between 5000 and 30,000 psi. The number of passes through the microfluidizer may vary in order to achieve the desired droplet size. The number of passes may be from about 2 to 20, 2 to 15, 4 to 15, 4 to 12 or 7 to 8.

[0115] The pharmaceutical formulation may then be passed through a filter system at room temperature, and/or autoclaved, to achieve sterilization. The filters used to achieve sterilization may be chosen by the skilled artisan and may have a nominal pore size of 0.2 μm. The filter material used may vary. In one embodiment, the filter is nylon. In another embodiment, the filter is a Posidyne® filter (covalent charge-modified Nylon 6,6 membrane which exhibits a net positively-charged zeta potential in aqueous solutions). For large scale production the method above may need to be

modified. A skilled practitioner could combine these materials in a different order and using different processing equipment to achieve the desired end result.

[0116] In one embodiment of the disclosure, the homogenization can be done in repeated cycles to achieve an emulsion in which the oil particle/globule size is less than 2 microns (μm) with intermediate cooling of the homogenized product to a temperature less than about 25 °C.

[0117] The final emulsion comprises an oil portion (oil phase) dispersed in an aqueous portion (aqueous phase). The ratio of components to the NK-1 receptor antagonist within the oil phase is an important characteristic of the emulsion which may affect stability of the formulation prepared for injection and each of these ratios within the final pharmaceutical emulsion are presented in more detail below. As described above, the oil phase comprises the NK-1 receptor antagonist, an oil and an emulsifier, examples of which are provided herein.

[0118] The final emulsion contains about 0.7 wt/wt% of the NK-1 receptor antagonist, but may range from about 0.2 wt/wt% to 1.5 wt/wt%, 0.4 wt/wt% to 1.0 wt/wt%, 0.6 wt/wt% to 0.7 wt/wt%, or 0.7 wt/wt% to 0.8 wt/wt%. The emulsion is prepared which can contain about 130 mg of the NK-1 receptor antagonist, however, preparations may also be prepared according to the present disclosure which contain about 100 mg to 1000 mg, 100 mg to 500 mg, 250 mg to 750 mg or 100 mg to 200 mg NK-1 receptor antagonist.

[0119] In one embodiment, the ratio of oil:NK-1 receptor antagonist (wt%:wt%) within the oil phase of the final emulsion is about 13:1 to 14:1, but can range from about 11:1 to 15:1, 12:1 to 14:1, 13:1 to 13.5:1, or 12:1 to 15:1. In another embodiment, the ratio of oil:NK-1 receptor antagonist is about 11:1, 11.5:1, 12:1, 12.5:1, 13:1, 13.5:1, 14:1, 14.5:1 or 15:1.

[0120] The ratio of emulsifier to NK-1 receptor antagonist in the final emulsion can be about 20:1 but may also vary. For example, the ratio of emulsifier:NK-1 receptor antagonist (wt%:wt%) within the oil portion ranges from about 15:1 to 30:1, 20:1 to 25:1, 18:1 to 22:1, 19:1 to 20:1, or 10:1 to 30:1. In one embodiment, the emulsifier:NK-1 receptor antagonist (wt%:wt%) is about 15:1, 18:1, 19:1, 20:1, 21:1, 22:1 or 23:1.

[0121] The ratio of components within the oil phase of the final emulsion may alternatively be expressed in the ratio of (emulsifier plus oil):NK-1 receptor antagonist (wt%:wt%). The ratio of (emulsifier plus oil):NK-1 receptor antagonist can be about 33:1, but the ratios for the present emulsion can range from about 20:1 to 40:1, 25:1 to 35:1, 30:1 to 35:1 or 33:1 to 37:1, or may be, for example, about 30:1, 32:1, 33:1, 34:1, 35:1, 36:1, 37:1, 38:1 or 40:1.

[0122] The composition of the present disclosure has a significant advantage in terms of reduced toxicity as compared to injectable formulations which may contain less desirable excipients such as detergents, e.g., Tween-20 or Tween-80. The present formulations take advantage of the ability to solubilize therapeutically effective amounts of a NK-1 receptor antagonist in an oil phase which can then be used to generate an emulsion suitable for injection. Accordingly, described herein are pharmaceutical emulsion compositions containing a NK-1 receptor antagonist and optionally dexamethasone or dexamethasone sodium phosphate, wherein the emulsion does not comprise a detergent.

[0123] The composition of the present disclosure gives a product suitable for parenteral use because of low particle size. The composition of the present disclosure is easy to use as the product can be diluted with an agent such as an aqueous solution of sucrose, an aqueous solution of maltose or dextrose 5% injection or normal saline to achieve the required concentration for parenteral administration. The composition of the present disclosure also has a prolonged shelf life and hence is suitable for a readily marketable product.

[0124] The compositions of the disclosure are both chemically and physically stable. A physically stable emulsion of the invention is one which can be stored under appropriate conditions for at least 1, 2, 3, 4, 5, 6, 9, 12, 15, 18, 24 or 36 months, without an increase in average droplet size above that allowed as stated in USP <729>. As well, the population of large-diameter fat globules should be within the limits stated in USP <729>.

[0125] Droplet size limits defined in USP <729> apply throughout the assigned shelf life, which for a commercial pharmaceutical formulation may extend to 2-3 years or longer. All true emulsions are thermodynamically unstable and may over time undergo a range of processes which tend to increase the droplet size. These include direct droplet coalescence, when two droplets collide and form a single new droplet, and aggregation, in which droplets adhere together to form larger masses. Aggregation may in some cases be a precursor of further coalescence into larger droplets. These processes may result in large aggregates rising to the surface of the container, a phenomenon known as 'creaming', and ultimately to free oil being visible on the emulsion surface, known as ‘cracking’.

[0126] Droplet size limits are typified by USP33-NF28 General Chapter <729> for Globule Size Distribution in Lipid Injectable Emulsions, hereinafter referred to as USP <729>, which defines universal limits for (1) mean droplet size not exceeding 500 nm or 0.5 μm and (2) the population of large-diameter fat globules, expressed as the volume-weighted percentage of fat greater than 5 μm (PFAT5) not exceeding 0.05%, irrespective of the final lipid concentration.

[0127] Droplet size measurements such as those defined in USP<729> can measure the initial increases in size, and hence are predictive of emulsion physical stability, at early times, long before the formulation shows macroscopic visible changes. Accordingly, the emulsions as described herein are stable compositions having an intensity-weighted mean droplet diameter less than about 500 nm, 400 nm, 300 nm, 200 nm or 100 nm.

[0128] The oil or particle droplet size, i.e. diameter, according to the present disclosure is measured using a dynamic light scattering (DLS) instrument, such as the Malvern Zetasizer 4000, Malvern Zetasize Nano S90 or preferably the Malvern Zetasizer Nano ZS. Intensity-weighted particles sizes were recorded, since they do not require the knowledge of the refractive index of the particle. In Malvern Zetasizer instruments, there are two fits for determining the intensity-weighted diameter of the oil droplet size. The first is a cumulant fit that is used to determine the Z-average diameter; this fit can additionally give the polydispersity index (PDI). This cumulant fit is recommended for monodisperse samples possessing a PDI of lower than 0.2. The second is a non-negative least squares (NNLS) fit. This gives the Peak 1 diameter, Peak 2 diameter and Peak 3 diameter. This is more suitable for polydisperse samples having a PDI of greater than 0.2.

[0129] The emulsion preparations as described herein may further comprise a preservative in quantities that preserve the composition. Suitable preservatives used in some of the embodiments of present disclosure include, but are not limited to, disodium edetate, tocopherol, benzalkonium chloride, methyl, ethyl, propyl or butylparaben, benzyl alcohol, phenylethyl alcohol, benzethonium, chlorobutanol, potassium sorbate or combination thereof.

III. MEDICAL USE

[0130] The pharmaceutical compositions of the present disclosure can be used for the prevention or treatment of emesis and provide a non-oral option for patients undergoing highly or moderately emetogenic chemotherapy such as chemotherapy used in cancer patients. The disclosure thus encompasses a method of treatment comprising intravenously administering an emulsion comprising a NK-1 receptor antagonist as described herein to a subject undergoing highly or moderately emetogenic chemotherapy whether the chemotherapy is an initial treatment or repeat courses of the chemotherapy. The pharmaceutical emulsions described herein can be used, for example, in preventing or treating acute and delayed nausea and vomiting associated with the chemotherapy or radiotherapy.

[0131] Another embodiment relates to the use of the pharmaceutical formulations of the disclosure in the manufacture of a medicament for use preventing or treating emesis in a subject in need thereof.

[0132] The amount of the NK-1 receptor antagonist and optionally dexamethasone required for use in the methods of the disclosure may vary with the method of administration and condition of the patient, and the degree of therapy required, and will be ultimately at the discretion of the attendant physician or clinician.

IV. EXAMPLES

The following examples are illustrative in nature and are in no way intended to be limiting.

Example 1: Preparing Aprepitant Emulsions for Intravenous Injection

[0133] To prepare the aprepitant emulsion, an oil phase was first prepared by combining 750 mg of aprepitant and 15.0 g of egg lecithin (LIPOID E 80) with 12.0 ml of ethanol. This mixture was dissolved by heating and stirring at 60 °C and 200 rpm for 15 min. To the resultant solution was added in 10.0 g of soybean oil. Heating at 60 ºC and stirring at 200 rpm was continued for another 15 min. The aqueous phase was prepared by dissolving 5.60 g of sucrose and 0.500 g of sodium oleate in 70.0 ml of water for injection. This mixture was stirred at 300 rpm at room temperature for 30 min. The aqueous phase was then added to the oil phase and subsequently subjected to high-speed homogenization (Ultra-Turrax® IKA T25) at a speed of 20,000 rpm for 1 min to produce the crude emulsion. This crude emulsion was then passed 8 times through an ice-cooled high-pressure microfluidizer (Microfluidizer® M-110L, F12Y interaction chamber) at a pressure of 18,000 psi. The resultant fine emulsion was sterilized by passing it through a 0.2 μm nylon syringe filter (Corning). The details of the emulsion composition are provided in Table 1 below. By dynamic light scattering (Malvern® Zetasizer Nano ZS), the intensity-weighted particle size analyzed using non-negative least squares (NNLS) fit gave a Peak 1 diameter of 99 nm. The intensity-weighted mean particle size determined using cumulant fit provided a Z-average diameter of 87 nm. The zeta potential was measured to be -43 mV by laser Doppler micro-electrophoresis (Malvern® Zetasizer Nano ZS). The pH of the injectable emulsion was 8.74. This aprepitant-containing emulsion can be injected as is, or diluted for infusion with 5% dextrose or 0.9% saline.

Table 1

Component	Amount (g)	Concentration (w/w%)	Ratio to Aprepitant
Aprepitant	0.750	0.679	1
Lipoid E 80	15.0	13.6	20
Soybean Oil	10.0	9.05	13.3
Ethanol[1]	8.59	7.78	11.5
Sucrose	5.60	5.07	7.5
Sodium Oleate	0.500	0.453	0.667
Water for Injection	70.0	63.4	93.3
Total	110	100	-

[1]Final amount after taking into account the ethanol that was evaporated during processing.

Example 2: Preparing Aprepitant Emulsions for Intravenous Injection

[0134] To prepare the aprepitant emulsion, an oil phase was first prepared by combining 450 mg of aprepitant and 9.00 g of egg lecithin (LIPOID E 80) with 4.0 ml of ethanol. This mixture was dissolved by heating and stirring at 60 °C and 200 rpm for 15 min. To the resultant solution was added 6.00 g of soybean oil. Heating at 60 °C and stirring at 200 rpm was continued for another 15 min. The aqueous phase was prepared by dissolving 3.36 g of sucrose and 0.300 g of sodium oleate in 42.0 ml of water for injection. This mixture was stirred at 300 rpm at room temperature for 30 min. The aqueous phase was then added to the oil phase and subsequently subjected to high-speed homogenization (Ultra-Turrax® IKA T25) at a speed of 20,000 rpm for 1 min to produce the crude emulsion. This crude emulsion was then passed 8 times through an ice-cooled high-pressure microfluidizer (Microfluidizer® M-110L, F12Y interaction chamber) at a pressure of 18,000 psi. The resultant fine emulsion was sterilized by passing it through a 0.2 μm nylon syringe filter (Corning). The details of the emulsion composition are provided in Table 2 below. By dynamic light scattering (Malvern® Zetasizer Nano ZS), the intensity-weighted particle size analyzed using NNLS fit gave a Peak 1 diameter of 127 nm. The intensity-weighted mean particle sized determined using cumulant fit provided a Z-average diameter of 101 nm. The zeta potential was measured to be -47 mV by laser Doppler micro-electrophoresis (Malvern® Zetasizer Nano ZS). The pH of the injectable emulsion was 8.77. This aprepitant-containing emulsion can be injected as is, or diluted for infusion with 5% dextrose or 0.9% saline.

Table 2

Component	Amount (g)	Concentration (w/w%)	Ratio to Aprepitant
Aprepitant	0.450	0.714	1
Lipoid E 80	9.00	14.3	20
Soybean Oil	6.00	9.52	13.3
Ethanol[1]	1.89	3.00	4.20
Sucrose	3.36	5.33	7.47
Sodium Oleate	0.300	0.476	0.667
Water for Injection	42.0	66.7	93.3
Total	63.0	100	-

[1]Final amount after taking into account the ethanol that was evaporated during processing.

Example 3: Preparing Aprepitant Emulsions for Intravenous Injection

[0135] To prepare the aprepitant emulsion, an oil phase was first prepared by combining 450 mg of aprepitant and 9.00 g of egg lecithin (LIPOID E 80) with 6.0 ml of ethanol. This mixture was dissolved by heating and stirring at 60 °C and 200 rpm for 15 min. To the resultant solution was added in 6.00 g of soybean oil. Heating at 60ºC and stirring at 200 rpm was continued for another 15 min. The aqueous phase was prepared by dissolving 15.62 g of sucrose and 0.300 g of sodium oleate in 42.0 ml of water for injection. This mixture was stirred at 300 rpm at room temperature for 30 min. The aqueous phase was then added to the oil phase and subsequently subjected to high-speed homogenization (Ultra-Turrax® IKA T25) at a speed of 20,000 rpm for 1 min to produce the crude emulsion. This crude emulsion was then passed 8 times through an ice-cooled high-pressure microfluidizer (Microfluidizer® M-110L, F12Y interaction chamber) at a pressure of 18,000 psi. The resultant fine emulsion was sterilized by passing it through a 0.2 μm nylon syringe filter (Corning). The details of the emulsion composition are provided in Table 3 below. By dynamic light scattering (Malvern® Zetasizer Nano ZS), the intensity-weighted particle size analyzed using NNLS fit gave a Peak 1 diameter of 88 nm. The intensity-weighted mean particle sized determined using cumulant fit provided a Z-average diameter of 68 nm. The zeta potential was measured to be -42 mV by laser Doppler micro-electrophoresis (Malvern® Zetasizer Nano ZS). The pH of the injectable emulsion was 8.80. This aprepitant-containing emulsion is to be diluted with water for injection by 4-fold prior to injection.

Table 3

Component	Amount (g)	Concentration (w/w%)	Ratio to Aprepitant
Aprepitant	0.450	0.587	1
Lipoid E 80	9.00	11.7	20
Soybean Oil	6.00	7.83	13.3
Ethanol[1]	3.27	4.26	7.26
Sucrose	15.6	20.4	34.7
Sodium Oleate	0.300	0.391	0.667
Water for Injection	42.0	54.8	93.3
Total	76.6	100	-

[1]Final amount after taking into account the ethanol that was evaporated during processing.

Example 4: Preparing an Alternate Aprepitant Emulsion Formulation for Intravenous Injection

[0136] An aprepitant emulsion was prepared which has less than 10% wt/wt of the phospholipid emulsifier and which was adjusted to a pH of less than 8.0. To prepare the aprepitant emulsion, an oil phase was first prepared by combining 450 mg of aprepitant and 6.67 g of egg lecithin (LIPOID E 80) with 7.2 ml of ethanol. This mixture was dissolved by heating and stirring at 60 °C and 200 rpm. Heating and stirring was carried out until the ethanol was evaporated and a thick residue was observed. To the resultant solution was added in 6.00 g of soybean oil and an appropriate amount of ethanol to obtain a clear oil phase upon heating at 60ºC. The aqueous phase was prepared by dissolving 3.36 g of sucrose in 50.5 ml of water for injection at 60ºC. The aqueous phase was then added to the oil phase and subsequently subjected to high-speed homogenization (Ultra-Turrax® IKA T25) at a speed of 20,000 rpm for 1 min to produce the crude emulsion. The pH of this crude emulsion was adjusted to 7.0 and then passed 8 times through an ice-cooled high-pressure microfluidizer (Microfluidizer® M-110L, F12Y interaction chamber) at a pressure of 18,000 psi. The resultant fine emulsion was sterilized by passing it through a 0.2 μm nylon syringe filter (Corning). The details of the emulsion composition are provided in Table 4 below. Within 4 days post preparation at room temperature, crystals were observed in the product by microscopy.

Table 4

Component	Amount (g)	Concentration (w/w%)	Ratio to Aprepitant
Aprepitant	0.450	0.672	1
Lipoid E 80	6.67	9.95	14.8
Soybean Oil	6.00	8.96	13.3
Sucrose	3.36	5.02	7.47
Water for Injection	50.5	75.4	112
Total	67.0	100	-

Example 5: Preparing Aprepitant Emulsions for Intravenous Injection

[0137] An aprepitant emulsion was prepared which contains oleic acid. To prepare the aprepitant emulsion, an oil phase was first prepared by combining 250 mg of aprepitant, 2.50 g of egg lecithin (LIPOID E 80), 15.0 g of soybean oil and 125 mg of oleic acid. Ten ml of ethanol was added to dissolve the mixture at 70 ºC. The ethanol was removed by pressure reduction in a 70 ºC water bath to yield a clear oil phase. A preheated aqueous phase containing 82.1 ml of water for injection at 70 ºC was added to the oil phase and subsequently subjected to high-speed homogenization (Ultra-Turrax® IKA T25) at a speed of 20,000 rpm for 1 min to produce the crude emulsion. This crude emulsion was passed 8 times through an ice-cooled high-pressure microfluidizer (Microfluidizer® M-110L, F12Y interaction chamber) at a pressure of 18,000 psi. The resultant fine emulsion was sterilized by passing it through a 0.2 µm nylon syringe filter (Corning). The details of the emulsion composition are provided in Table 5 below. Within 4 days post-preparation at room temperature, crystals were observed in the product by microscopy.

Table 5

Component	Amount (g)	Concentration (w/w%)	Ratio to aprepitant
Aprepitant	0.250	0.250	1
Lipoid E 80	2.50	2.50	10
Soybean Oil	15.0	15.0	60
Oleic Acid	0.125	0.125	0.5
Water for Injection	82.1	82.1	328
Total	100	100	-

Example 6: Preparing Emulsions Containing Aprepitant and Dexamethasone Sodium Phosphate for Intravenous Injection

[0138] To prepare an injectable emulsion containing aprepitant and dexamethasone sodium phosphate, an oil phase was first prepared by combining 773 mg of aprepitant and 15.5 g of egg lecithin (LIPOID E 80) with 10.3 ml of ethanol. This mixture was dissolved by heating and stirring at 60 °C and 200 rpm for 15 min. To the resultant solution was added in 10.3 g of soybean oil. Heating at 60 ºC and stirring at 200 rpm was continued for another 15 min. The aqueous phase was prepared by dissolving 5.77 g of sucrose and 0.515 g of sodium oleate in 71.1 ml of water for injection. This mixture was stirred at 300 rpm at room temperature for 30 min. The aqueous phase was then added to the oil phase and subsequently subjected to high-speed homogenization (Ultra-Turrax® IKA T25) at a speed of 20,000 rpm for 1 min to produce the crude emulsion. This crude emulsion was then passed 8 times through an ice-cooled high-pressure microfluidizer (Microfluidizer® M-110L, F12Y interaction chamber) at a pressure of 18,000 psi. Dexamethasone sodium phosphate (93.5 mg) dissolved in 1 ml of water for injection was mixed into the fine emulsion. This resultant fine emulsion containing both aprepitant and dexamethasone sodium phosphate was sterilized by passing it through a 0.2 μm nylon syringe filter (Corning). The details of the emulsion composition are provided in Table 6 below. By dynamic light scattering (Malvern® Zetasizer Nano ZS), the intensity-weighted particle size analyzed using NNLS fit gave a Peak 1 diameter of 95 nm. The intensity-weighted mean particle size determined using cumulant fit provided a Z-average diameter of 70 nm. The zeta potential was measured to be -43 mV by laser Doppler micro-electrophoresis (Malvern® Zetasizer Nano ZS). The pH of the injectable emulsion was 8.92. This aprepitant and dexamethasone sodium phosphate containing emulsion can be injected as is, or diluted for infusion with 5% dextrose or 0.9% saline.

Table 6

Component	Amount (g)	Concentration (w/w%)	Ratio to aprepitant
Aprepitant	0.773	0.688	1
Dexamethasone Sodium Phosphate	0.0935	0.0832	0.121
Lipoid E 80	15.5	13.8	20
Soybean Oil	10.3	9.17	13.3
Ethanol[1]	7.31	6.51	9.47
Sucrose	5.77	5.14	7.47
Sodium Oleate	0.515	0.459	0.667
Water for Injection	72.1	64.2	93.3
Total	112	100	-

[1]Final amount after taking into account the ethanol that was evaporated during processing.

Example 7: Stability of the Aprepitant Emulsion at Room Temperature and 5 °C

[0139] Stability of the aprepitant emulsions prepared as described in Examples 1, 2 3 and 6 was measured by incubating each emulsion preparation at room temperature (about 25 °C) or at 5 °C. Mean particle size and percentage of fat globules above 5 μm were measured using DLS and light obscuration respectively to determine if they satisfy USP <729>. The emulsions were also inspected by microscopy for aprepitant crystals. Example 1 was stable at room temperature for 2 months, that is, the mean particle size and percentage of fat globules above 5 μm satisfied USP <729>. Additionally, no aprepitant crystals were visible by microscopy. After 2 months storage at room temperature, creaming was observed in Examples 1 and 6. This corresponded with the observation of aprepitant crystals. Examples 2 and 3 were stable at room temperature for 3 and 2 months respectively. After these time points, aprepitant crystals were observed in these formulations. Storage at 5 ºC resulted in longer emulsion stability for Examples 1, 2, 3 and 6. Table 7 shows the characterizations of Examples 1, 2, 3 and 6 and their respective stabilities at room temperature and at 5 ºC.

Table 7

Sample	PDI	Particle Size as Peak 1 Diameter (nm)	Particle Size as Z-Average Diameter (nm)	Zeta Potential (mV)	pH	Stability at 25 °C per USP <729> (months)	Stability at 5 °C per USP <729>
Example 1	0.122	99	87	-43	8.74	2	>10 months
Example 2	0.200	127	101	-47	8.77	3	>10 months
Example 3	0.219	88	68	-42	8.80	2	>10 months
Example 6	0.244	95	70	-43	8.92	2	>10 months

Example 8: Stability of the Aprepitant Emulsion to Freeze-Thaw Cycle

[0140] The aprepitant emulsions prepared according to Examples 1, 2, 3 and 6 were tested for stability upon exposure to a freeze-thaw cycle. Samples from the Examples 1, 2, 3 and 6 were stored at -20 °C overnight. They were thawed to room temperature the next day and visualized by microscopy. Prior to freezing, all samples did not present any visible particles under the microscope. FIG. 1 shows microscope images, at 10X, of emulsions after the freeze-thaw cycle (Examples 1, 2, 3 and 6 are shown as FIG. 1 A, B, C, and D, respectively). Emulsions prepared as described in examples 1, 2 and 6 showed visible particles after exposure to freezing. Only Example 3 was stable after freezing. As FIG. 1C shows, no visible particles were observed for the formulation of Example 3. This enhanced stability was conferred by the presence of a large concentration of sucrose (20 w/w% in Example 3 compared to 5 w/wt% in Examples 1, 2 and 6).

Example 9: Pharmacokinetics of an Aprepitant Emulsion

[0141] The pharmacokinetics of an aprepitant emulsion prepared according to Example 1 was determined. Two groups of six male Sprague-Dawley rats each were injected intravenously with, respectively, fosaprepitant in solution or aprepitant emulsion prepared according to Example 1. All drugs were administered at an effective concentration equivalent to 14 mg/kg aprepitant. Blood from all rats was collected at the appropriate time intervals and processed to plasma by centrifugation. Plasma samples were analyzed by LC-MS/MS for aprepitant and fosaprepitant, as appropriate. A plasma concentration versus time curve of aprepitant for the emulsion described in Example 1 and for fosaprepitant is presented in FIG. 2 (fosaprepitant in solution, ●; aprepitant emulsion, ▲). The

curves indicate the initial aprepitant level reached immediately after injection of the aprepitant emulsion was almost 3 times higher than the initial aprepitant level reached immediately after injection of the fosaprepitant solution. Plasma levels of aprepitant resulting from each injection, however, were essentially the same by the 3-hour time point indicating the formulations were bioequivalent except for a delay in the conversion of fosaprepitant to aprepitant.

Example 10: Pharmacokinetics of an Aprepitant and Dexamethasone Emulsion

[0142] The pharmacokinetics of an aprepitant and dexamethasone sodium phosphate combination emulsion prepared according to Example 6 was determined. Male Sprague-Dawley rats each were injected intravenously with fosaprepitant solution (group 1), dexamethasone sodium phosphate solution (group 2), or an emulsion containing aprepitant and dexamethasone sodium phosphate prepared according to Example 6 (group 3). Groups 1 and 2 consisted of six rats each; for group 3, twelve rats were injected with the aprepitant and dexamethasone sodium phosphate combination emulsion to allow for the collection of sufficient samples for the measurement of both active ingredients.

[0143] In groups 1 and 3, a dose was administered at an effective drug concentration equivalent to 2 mg/kg aprepitant. In groups 2 and 3, a dose was administered at an effective drug concentration equivalent to 0.24 mg/kg dexamethasone sodium phosphate. Blood from all rats was collected at the appropriate time intervals and processed to plasma by centrifugation. Plasma samples were analyzed by LC-MS/MS for dexamethasone, aprepitant, and fosaprepitant, as appropriate.

[0144] FIGS. 3 and 4 present the plasma concentration versus time curve of aprepitant and dexamethasone, respectively. FIG. 3 compares the aprepitant plasma concentration versus time curve resulting from injection of the emulsion described in Example 6 (FIG. 3, ●) vs. injection of a solution of fosaprepitant (FIG. 3, ▲). FIG. 4 compares the dexamethasone plasma concentration versus time curve resulting from injection of a dexamethasone sodium phosphate solution (FIG. 4, ●) vs. injection of the emulsion described in Example 6. The curves indicate that the aprepitant in the emulsion is released approximately simultaneously with the dexamethasone sodium phosphate. The presence of dexamethasone sodium phosphate in the emulsion does not affect the pharmacokinetics of aprepitant.

Example 11: Preparing Aprepitant Emulsions for Intravenous Injection

[0145] To prepare the aprepitant emulsion comprising a buffering agent, an oil phase is first prepared by combining 750 mg of aprepitant, 15.0 g of egg lecithin (LIPOID E 80), 10.0 g of soybean oil and 3.75 ml of ethanol. This mixture is dissolved by heating and stirring at 70 °C and 200 rpm for

30 min. The aqueous phase is prepared by dissolving 2.17 g of sucrose and 0.500 g of sodium oleate in a mixture of 4.1 ml of 1M Tris buffer (pH 8.4) and 65.9 ml of water for injection. This mixture is stirred at 300 rpm at room temperature for 30 min. The aqueous phase is then added to the oil phase and subsequently subjected to high-speed homogenization (Ultra-Turrax® IKA T25) at a speed of 20,000 rpm for 1 min to produce the crude emulsion. This crude emulsion is then passed 8 times through an ice-cooled high-pressure microfluidizer (Microfluidizer® M-110L, F12Y interaction chamber) at a pressure of 18,000 psi. The resultant fine emulsion is sterilized by passing it through a 0.2 μm nylon syringe filter (Corning). Dynamic light scattering is used to determine the intensity-weighted particle size using NNLS fit to give the Peak 1 diameter, the intensity-weighted mean particle sized is determined using cumulant fit to provide the Z-average diameter. The zeta potential is measured by laser Doppler micro-electrophoresis (Malvern® Zetasizer Nano ZS). This aprepitant-containing emulsion can be injected as is, or diluted for infusion with 5% dextrose or 0.9% saline.

Example 12: Preparing Rolapitant Emulsions for Intravenous Injection

[0146] To prepare the rolapitant emulsion, an oil phase was first prepared by combining 1.080 g of rolapitant and 21.6 g of egg lecithin (LIPOID E 80) with 14.4 g of soybean oil and 5.40 ml of ethanol in a glass jar. This mixture was allowed to incubate at room temperature for 30 min followed by heating and stirring at 70°C and 200 rpm for another 30 min. The aqueous phase was prepared by dissolving 8.06 g of sucrose and 0.720 g of sodium oleate in 100.8 ml of water for injection by heating and stirring at 35°C and 300 rpm for 15 min. The aqueous phase was then added to the oil phase and subsequently subjected to high-speed homogenization (Ultra-Turrax® IKA T25) at a speed of 20,000 rpm for 1 min to produce the crude emulsion. This crude emulsion was passed 8 times through a high-pressure microfluidizer (Microfluidizer® M-110P, F12Y interaction chamber) at a pressure of 20,000 psi. The outlet fine emulsion temperature was kept at approximately 25°C using cooling water. The resultant fine emulsion was sterilized by passing through a 0.2 μm nylon filter (Nalgene). Details of the emulsion composition are provided in Table 8 below. By dynamic light scattering (Malvern® Zetasizer Nano ZS), the intensity-weighted particle size analyzed using non-negative least squares (NNLS) fit gave a Peak 1 diameter of 127 nm (Table 9). The intensity-weighted mean particle size determined using cumulant fit provided a Z-average diameter of 100 nm. The pH and osmolality of the injectable emulsion were 8.51 and 318 mmol/kg respectively. This rolapitant-containing emulsion can be injected as is, or diluted for infusion with 0.9% saline or 5% dextrose.

Table 8

Component	Amount (g)	Concentration (w/w%)	Ratio to Rolapitant
Rolapitant	1.080	0.728	1
Lipoid E 80	21.6	14.55	20
Soybean Oil	14.4	9.70	13.3
Ethanol[1]	1.78	1.20	1.65
Sucrose	8.06	5.43	7.47
Sodium Oleate	0.720	0.485	0.667
Water for Injection	100.8	67.9	93.3
Total	148	100	-

[1]Final amount after taking into account the ethanol that was evaporated during processing.

Table 9

Sample	PDI	Particle Size as Peak 1 Diameter (nm)	Particle Size as Z-Average Diameter (nm)	pH	Osmolality (mmol/kg)	Stability at 25ºC per USP <729>	Stability at 5ºC per USP <729>
Example 1	0.213	127	100	8.51	318	>1 months	>1 months

Example 13: Preparing Netupitant Emulsions for Intravenous Injection

[0147] To prepare the emulsion containing a therapeutically effective amount of netupitant, an oil phase is first prepared by combining about 750 mg of netupitant and 15.0 g of egg lecithin (LIPOID E 80) with 12.0 ml of ethanol. This mixture is dissolved by heating and stirring at 60 ℃ and 200 rpm for 15 min. To the resultant solution is added in 10.0 g of soybean oil. Heating at 60 ºC and stirring at 200 rpm is continued for another 15 min. The aqueous phase is prepared by dissolving 5.60 g of sucrose and 0.500 g of sodium oleate in 70.0 ml of water for injection. This mixture is stirred at 300 rpm at room temperature for 30 min. The aqueous phase is then added to the oil phase and subsequently subjected to high-speed homogenization (Ultra-Turrax® IKA T25) at a speed of 20,000 rpm for 1 min to produce the crude emulsion. This crude emulsion is then passed 8 times through an ice-cooled high-pressure microfluidizer (Microfluidizer® M-110L, F12Y interaction chamber) at a pressure of 18,000 psi. The resultant fine emulsion is sterilized by passing it through a 0.2 μm nylon syringe filter (Corning). The details of the emulsion composition are provided in Table 10 below. By dynamic light scattering (Malvern® Zetasizer Nano ZS), the intensity-weighted particle size is analyzed using non-negative least squares (NNLS) fit to obtain a Peak 1 diameter of the particle. The intensity-weighted mean particle size is also determined using cumulant fit and provides a Z-average

diameter. The zeta potential is measured to be -43 mV by laser Doppler micro-electrophoresis (Malvern® Zetasizer Nano ZS). The pH of the injectable emulsion is also measured and is preferably about pH 7.8 to 8.8. This NK-1 receptor antagonist-containing emulsion can be injected as is, or diluted for infusion with 5% dextrose or 0.9% saline.

Table 10

Component	Amount (g)	Concentration (w/w%)	Ratio to Netupitant
Netupitant	0.750	0.679	1
Lipoid E 80	15.0	13.6	20
Soybean Oil	10.0	9.05	13.3
Ethanol[1]	8.59	7.78	11.5
Sucrose	5.60	5.07	7.5
Sodium Oleate	0.500	0.453	0.667
Water for Injection	70.0	63.4	93.3
Total	110	100	-

[1]Final amount after taking into account the ethanol that is evaporated during processing.

Example 14: Preparing Netupitant Emulsions for Intravenous Injection

[0148] To prepare the netupitant emulsion, an oil phase is first prepared by combining about 450 mg of netupitant and 9.00 g of egg lecithin (LIPOID E 80) with 4.0 ml of ethanol. This mixture is dissolved by heating and stirring at 60 °C and 200 rpm for 15 min. To the resultant solution is added 6.00 g of soybean oil. Heating at 60 ºC and stirring at 200 rpm is continued for about another 15 min. The aqueous phase is prepared by dissolving 3.36 g of sucrose and 0.300 g of sodium oleate in 42.0 ml of water for injection. This mixture is stirred at 300 rpm at room temperature for 30 min. The aqueous phase is then added to the oil phase and subsequently subjected to high-speed homogenization (Ultra-Turrax® IKA T25) at a speed of 20,000 rpm for 1 min to produce the crude emulsion. This crude emulsion is then passed 8 times through an ice-cooled high-pressure microfluidizer (Microfluidizer® M-110L, F12Y interaction chamber) at a pressure of 18,000 psi. The resultant fine emulsion is sterilized by passing it through a 0.2 µm nylon syringe filter (Corning). The details of the emulsion composition are provided in Table 11 below. By dynamic light scattering (Malvern® Zetasizer Nano ZS), the intensity-weighted particle size is analyzed using NNLS fit to give a Peak 1 diameter. The intensity-weighted mean particle size is determined using cumulant fit provides a Z-average diameter. The zeta potential is measured by laser Doppler micro-electrophoresis (Malvern® Zetasizer Nano ZS). The pH of the injectable emulsion is also measured and is preferably

about pH 7.8 to 8.8. This netupitant-containing emulsion can be injected as is, or diluted for infusion with 5% dextrose or 0.9% saline.

Table 11

Component	Amount (g)	Concentration (w/w%)	Ratio to Netupitant
Netupitant	0.450	0.714	1
Lipoid E 80	9.00	14.3	20
Soybean Oil	6.00	9.52	13.3
Ethanol[1]	1.89	3.00	4.20
Sucrose	3.36	5.33	7.47
Sodium Oleate	0.300	0.476	0.667
Water for Injection	42.0	66.7	93.3
Total	63.0	100	-

[1]Final amount after taking into account the ethanol that is evaporated during processing.

Example 15: Preparing Netupitant Emulsions for Intravenous Injection

[0149] To prepare the netupitant emulsion, an oil phase is first prepared by combining 450 mg of netupitant and 9.00 g of egg lecithin (LIPOID E 80) with 6.0 ml of ethanol. This mixture is dissolved by heating and stirring at 60 °C and 200 rpm for 15 min. To the resultant solution is added in 6.00 g of soybean oil. Heating at 60ºC and stirring at 200 rpm is continued for another 15 min. The aqueous phase is prepared by dissolving 15.62 g of sucrose and 0.300 g of sodium oleate in 42.0 ml of water for injection. This mixture is stirred at 300 rpm at room temperature for 30 min. The aqueous phase is then added to the oil phase and subsequently subjected to high-speed homogenization (Ultra-Turrax® IKA T25) at a speed of 20,000 rpm for 1 min to produce the crude emulsion. This crude emulsion is then passed 8 times through an ice-cooled high-pressure microfluidizer (Microfluidizer® M-110L, F12Y interaction chamber) at a pressure of 18,000 psi. The resultant fine emulsion is sterilized by passing it through a 0.2 μm nylon syringe filter (Corning). The details of the emulsion composition are provided in Table 12 below. By dynamic light scattering (Malvern® Zetasizer Nano ZS), the intensity-weighted particle size is analyzed using NNLS fit gave a Peak 1 diameter. The intensity-weighted mean particle size is determined using cumulant fit provided a Z-average diameter. The zeta potential is measured by laser Doppler micro-electrophoresis (Malvern® Zetasizer Nano ZS). The pH of the injectable emulsion is also measured and is preferably about pH 7.8 to 8.8. This netupitant-containing emulsion is to be diluted with water for injection by 4-fold prior to injection.

Table 12

Component	Amount (g)	Concentration (w/w%)	Ratio to Netupitant
Netupitant	0.450	0.587	1
Lipoid E 80	9.00	11.7	20
Soybean Oil	6.00	7.83	13.3
Ethanol[1]	3.27	4.26	7.26
Sucrose	15.6	20.4	34.7
Sodium Oleate	0.300	0.391	0.667
Water for Injection	42.0	54.8	93.3
Total	76.6	100	-

[1]Final amount after taking into account the ethanol that is evaporated during processing.

Example 16: Alternate Netupitant Emulsion Formulations for Intravenous Injection

[0150] A netupitant emulsion is prepared which has less than 10% wt/wt of the phospholipid emulsifier and which is adjusted to a pH of less than 8.0. To prepare the netupitant emulsion, an oil phase is first prepared by combining 450 mg of netupitant and 6.67 g of egg lecithin (LIPOID E 80) with 7.2 ml of ethanol. This mixture is dissolved by heating and stirring at 60 °C and 200 rpm. Heating and stirring is carried out until the ethanol is evaporated and a thick residue is observed. To the resultant solution is added in 6.00 g of soybean oil and an appropriate amount of ethanol to obtain a clear oil phase upon heating at 60ºC. The aqueous phase is prepared by dissolving 3.36 g of sucrose in 50.5 ml of water for injection at 60ºC. The aqueous phase is then added to the oil phase and subsequently subjected to high-speed homogenization (Ultra-Turrax® IKA T25) at a speed of 20,000 rpm for 1 min to produce the crude emulsion. The pH of this crude emulsion is adjusted to 7.0 and then passed 8 times through an ice-cooled high-pressure microfluidizer (Microfluidizer® M-110L, F12Y interaction chamber) at a pressure of 18,000 psi. The resultant fine emulsion is sterilized by passing it through a 0.2 µm nylon syringe filter (Corning). The details of the emulsion composition are provided in Table 13 below. Within 4 days post preparation at room temperature, the emulsion product is analyzed for the presence of crystals by microscopy.

Table 13

Component	Amount (g)	Concentration (w/w%)	Ratio to Netupitant
Netupitant	0.450	0.672	1

Lipoid E 80	6.67	9.95	14.8
Soybean Oil	6.00	8.96	13.3
Sucrose	3.36	5.02	7.47
Water for Injection	50.5	75.4	112
Total	67.0	100	-

Example 17: Alternate Netupitant Emulsion Formulations for Intravenous Injection

[0151] A netupitant emulsion is prepared which contains oleic acid. To prepare the netupitant emulsion, an oil phase is first prepared by combining 250 mg of netupitant, 2.50 g of egg lecithin (LIPOID E 80), 15.0 g of soybean oil and 125 mg of oleic acid. Ten ml of ethanol is added to dissolve the mixture at 70 ºC. The ethanol is removed by pressure reduction in a 70 ºC water bath to yield a clear oil phase. A preheated aqueous phase containing 82.1 ml of water for injection at 70 ºC is added to the oil phase and subsequently subjected to high-speed homogenization (Ultra-Turrax® IKA T25) at a speed of 20,000 rpm for 1 min to produce the crude emulsion. This crude emulsion is passed 8 times through an ice-cooled high-pressure microfluidizer (Microfluidizer® M-110L, F12Y interaction chamber) at a pressure of 18,000 psi. The resultant fine emulsion is sterilized by passing it through a 0.2 µm nylon syringe filter (Corning). The details of the emulsion composition are provided in Table 14 below. Within 4 days post preparation at room temperature, the emulsion product is analyzed for the presence of crystals by microscopy.

Table 14

Component	Amount (g)	Concentration (w/w%)	Ratio to Netupitant
Netupitant	0.250	0.250	1
Lipoid E 80	2.50	2.50	10
Soybean Oil	15.0	15.0	60
Oleic Acid	0.125	0.125	0.5
Water for Injection	82.1	82.1	328
Total	100	100	-

Example 18: Preparing Emulsions Containing Netupitant and Dexamethasone Sodium Phosphate for Intravenous Injection

[0152] To prepare an injectable emulsion containing netupitant and dexamethasone sodium phosphate, an oil phase are first prepared by combining 773 mg of netupitant and 15.5 g of egg lecithin (LIPOID E 80) with 10.3 ml of ethanol. This mixture is dissolved by heating and stirring at 60 °C and 200 rpm for 15 min. To the resultant solution is added in 10.3 g of soybean oil. Heating at 60 °C and stirring at 200 rpm is continued for another 15 min. The aqueous phase is prepared by dissolving 5.77 g of sucrose and 0.515 g of sodium oleate in 71.1 ml of water for injection. This mixture is stirred at 300 rpm at room temperature for 30 min. The aqueous phase is then added to the oil phase and subsequently subjected to high-speed homogenization (Ultra-Turrax® IKA T25) at a speed of 20,000 rpm for 1 min to produce the crude emulsion. This crude emulsion is then passed 8 times through an ice-cooled high-pressure microfluidizer (Microfluidizer® M-110L, F12Y interaction chamber) at a pressure of 18,000 psi. Dexamethasone sodium phosphate (93.5 mg) dissolved in 1 ml of water for injection is mixed into the fine emulsion. This resultant fine emulsion containing both netupitant and dexamethasone sodium phosphate is sterilized by passing it through a 0.2 μm nylon syringe filter (Corning). The details of the emulsion composition are provided in Table 15 below. By dynamic light scattering (Malvern® Zetasizer Nano ZS), the intensity-weighted particle size is analyzed using NNLS fit to determine a Peak 1 diameter. The intensity-weighted mean particle size is determined using cumulant fit to determine a Z-average diameter. The zeta potential is measured to be -43 mV by laser Doppler micro-electrophoresis (Malvern® Zetasizer Nano ZS). The preferred pH of the injectable emulsion is between about 8.5 and 9.5. This netupitant and dexamethasone sodium phosphate containing emulsion can be injected as is, or diluted for infusion with 5% dextrose or 0.9% saline.

Table 15

Component	Amount (g)	Concentration (w/w%)	Ratio to Netupitant
Netupitant	0.773	0.688	1
Dexamethasone Sodium Phosphate	0.0935	0.0832	0.121
Lipoid E 80	15.5	13.8	20
Soybean Oil	10.3	9.17	13.3
Ethanol[1]	7.31	6.51	9.47
Sucrose	5.77	5.14	7.47
Sodium Oleate	0.515	0.459	0.667
Water for Injection	72.1	64.2	93.3
Total	112	100	-

[1]Final amount after taking into account the ethanol that is evaporated during processing.

Example 19: Preparing NK-1 Receptor Antagonist Emulsions for Intravenous Injection

[0153] To prepare an NK-1 receptor antagonist emulsion comprising a buffering agent, an oil phase is first prepared by combining 750 mg of aprepitant, 15.0 g of egg lecithin (LIPOID E 80), 10.0 g of soybean oil and 3.75 ml of ethanol. This mixture is dissolved by heating and stirring at 70 °C and 200 rpm for 30 min. The aqueous phase is prepared by dissolving 2.17 g of sucrose and 0.500 g of sodium oleate in a mixture of 4.1 ml of 1M Tris buffer (pH 8.4) and 65.9 ml of water for injection. This mixture is stirred at 300 rpm at room temperature for 30 min. The aqueous phase is then added to the oil phase and subsequently subjected to high-speed homogenization (Ultra-Turrax® IKA T25) at a speed of 20,000 rpm for 1 min to produce the crude emulsion. This crude emulsion is then passed 8 times through an ice-cooled high-pressure microfluidizer (Microfluidizer® M-110L, F12Y interaction chamber) at a pressure of 18,000 psi. The resultant fine emulsion is sterilized by passing it through a 0.2 μm nylon syringe filter (Corning). Dynamic light scattering is used to determine the intensity-weighted particle size using NNLS fit to give the Peak 1 diameter, the intensity-weighted mean particle sized is determined using cumulant fit to provide the Z-average diameter. The zeta potential is measured by laser Doppler micro-electrophoresis (Malvern® Zetasizer Nano ZS). This aprepitant-containing emulsion can be injected as is, or diluted for infusion with 5% dextrose or 0.9% saline.

Example 20: Stability of the Rolapitant Emulsion at Room Temperature and 5 °C

[0154] Stability of the rolapitant emulsion prepared as described in Example 12 was measured by incubating the emulsion preparation at room temperature (about 25 °C) or at 5 °C. Mean particle size and percentage of fat globules above 5 μm were measured using DLS and light obscuration respectively and demonstrated to satisfy USP <729> after 2 months of storage. The emulsions were also inspected by microscopy for rolapitant crystals and visually for the presence of emulsion creaming. The absence of crystals or emulsion creaming further indicated product stability.

Example 21: Stability of the Netupitant Emulsion at Room Temperature and 5 °C

[0155] Stability of the netupitant emulsions prepared as described in Examples 13-17 can be measured by incubating each emulsion preparation at room temperature (about 25 °C) or at 5 °C. Mean particle size and percentage of fat globules above 5 μm are measured using DLS and light obscuration respectively to determine if they satisfy USP <729>. The emulsions are also inspected by microscopy for netupitant crystals and/or visually for the presence of emulsion creaming. The absence of crystals or emulsion creaming indicates product stability.

Example 22: Stability of the Netupitant Emulsion to Freeze-Thaw Cycle

[0156] The netupitant emulsions prepared according to Examples 13-17 can be tested for stability upon exposure to a freeze-thaw cycle. Samples from the Examples 13-17 are stored at -20 ºC overnight. The absence of visible particles when the samples are viewed under a microscope indicates product stability.

[0157] While a number of exemplary aspects and embodiments have been discussed above, those of skill in the art will recognize certain modifications, permutations, additions and sub-combinations thereof. It is therefore intended that the following appended claims and claims hereafter introduced are interpreted to include all such modifications, permutations, additions and sub-combinations as are within their true spirit and scope.

WHAT IS CLAIMED IS:

1. An injectable pharmaceutical emulsion, comprising:
about 0.7-0.8 wt% aprepitant;
an emulsifier;
an oil;
a co-surfactant; and
water,
wherein the ratio of the emulsifier to aprepitant ranges from about 20:1 to 25:1 (wt/wt%).

2. The emulsion of claim 1, wherein the emulsifier is a phospholipid.

3. The emulsion of claim 2, wherein the phospholipid is present in the emulsion at about 16 wt/wt%.

4. The emulsion of claim 2, wherein the phospholipid is present in the emulsion at about 17 wt/wt%.

5. The emulsion of claim 1, wherein the emulsifier is an egg lecithin.

6. The emulsion of claim 5, wherein the egg lecithin is present in the emulsion at about 16 wt/wt%.

7. The emulsion of claim 5, wherein the phospholipid is present in the emulsion at about 17 wt/wt%.

8. The emulsion of claim 1, wherein the oil is selected from the group consisting of coconut oil, olive oil, soybean oil, safflower oil, triglycerides, octyl and decyl glycerate, ethyl oleate, glyceryl linoleate, ethyl linoleate, glyceryl oleate, cholesteryl oleate, cholesteryl linoleate, and mixtures thereof.

9. The emulsion of claim 8, wherein the oil is present at a concentration of about 9 wt/wt % to 10 wt/wt %.

10. The emulsion of claim 1, wherein the co-surfactant comprises an alcohol.

11. The emulsion of claim 10, wherein the alcohol is present in the emulsion at less than 10 wt/wt%.

12. The emulsion of claim 10, wherein the co-surfactant is ethanol.

13. The emulsion of claim 1, further comprising an osmotic agent.

14. The emulsion of claim 13, wherein the osmotic agent is selected from the group consisting of glycerol, sorbitol, xylitol, mannitol, glucose, trehalose, maltose, sucrose, raffinose, lactose, dextran, polyethylene glycol, or propylene glycol.

15. The emulsion of claim 14, wherein the osmotic agent is present at a concentration of about 3 wt/wt % to 8 wt/wt %.

16. The emulsion of claim 1, further comprising a pH modifier.

17. The emulsion of claim 16, wherein the pH modifier is oleic acid or a salt thereof.

18. The emulsion of claim 1, wherein the emulsifier is egg lecithin.

19. The emulsion of claim 1, wherein the co-surfactant is ethanol.

20. The emulsion of claim 1, further comprising sucrose.

21. The emulsion of claim 1, further comprising sodium oleate

22. An injectable pharmaceutical emulsion, comprising:
about 0.7-0.8 wt% aprepitant;
an emulsifier;
an oil;
a co-surfactant; and
water,
wherein the ratio of the emulsifier to aprepitant ranges about 23:1 (wt/wt%).

23. The emulsion of claim 22, wherein the emulsifier is a phospholipid.

24. The emulsion of claim 23, wherein the phospholipid is selected from the group consisting of egg phospholipids and soy phospholipids.

25. The emulsion of claim 22, wherein the oil is selected from the group consisting of coconut oil, olive oil, soybean oil, safflower oil, triglycerides, octyl and decyl glycerate, ethyl oleate, glyceryl linoleate, ethyl linoleate, glyceryl oleate, cholesteryl oleate, cholesteryl linoleate, and mixtures thereof.

26. The emulsion of claim 22, wherein the co-surfactant comprises an alcohol present in the emulsion at less than 10 wt/wt%.

27. An injectable pharmaceutical emulsion, comprising:
about 0.7-0.8 wt% aprepitant;
an emulsifier;
an oil;
a co-surfactant; and
water,
wherein the ratio of the emulsifier to aprepitant ranges about 24:1 (wt/wt%).

28. The emulsion of claim 27, wherein the emulsifier is a phospholipid.

29. The emulsion of claim 27, wherein the phospholipid is selected from the group consisting of egg phospholipids and soy phospholipids.

30. The emulsion of claim 27, wherein the oil is selected from the group consisting of coconut oil, olive oil, soybean oil, safflower oil, triglycerides, octyl and decyl glycerate, ethyl oleate, glyceryl linoleate, ethyl linoleate, glyceryl oleate, cholesteryl oleate, cholesteryl linoleate, and mixtures thereof.

ABSTRACT OF THE DISCLOSURE

Disclosed herein are novel pharmaceutical formulations of a neurokinin-1 (NK-1) receptor antagonist suitable for parenteral administration including intravenous administration. Also included are formulations including both the NK-1 receptor antagonist and dexamethasone sodium phosphate. The pharmaceutical formulations are stable oil-in-water emulsions for non-oral treatment of emesis and are particularly useful for treatment of subjects undergoing highly emetogenic cancer chemotherapy.

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EXAMINER	
LEVIN, MIRIAM A	

ART UNIT	PAPER NUMBER
1613	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mweipdocket@mwe.com

Applicant-Initiated Interview Summary	Application No.	Applicant(s)	
	15/083,071	OTTOBONI ET AL.	
	Examiner	Art Unit	
	MIRIAM A. LEVIN	1613	

All participants (applicant, applicant's representative, PTO personnel):

(1) *MIRIAM A. LEVIN*.

(2) *Dr. Susan Harlocker, patent agent*.

(3) *Dr. Tom Ottoboni, named inventor, Sr. VP R&D*.

(4)_____.

Date of Interview: *25 August 2016*.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☒ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☐112 ☐102 ☒103 ☐Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: *1*.

Identification of prior art discussed: *Zhou (cited in office action)*.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

See Continuation Sheet.

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☒ Attachment

/ANNA PAGONAKIS/ Primary Examiner, Art Unit 1628	

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews
Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

Continuation of Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: Agreement: Applicant does not need to amend the claims to recite functional limitations. The Examiner will issue this interview summary and Applicant will file a response.

Following is a summary of the discussion. This summary is NOT intended to indicate that agreement was reached on any issue other than as explicitly indicated.

Dr. Harlocker advised that Ex. 4 in the specification can be compared to the invention of Zhou. The Examiner sought clarification regarding the process described in Ex. 4 of the specification vs. the examples of Zhou. The Examiner suggested that Dr. Ottoboni provide a Declaration to explain any differences in the procedure of Ex. 4 vs.the process used in Zhou. (e.g. Zhou Ex. 1 uses the term "coarse emulsion" but does not have 2 phases at that point, Zhou Ex. 1 appears to dissolve the "sticky residue with soybean oil and ethanol before heating, but Ex. 4 of the spec. appears to require heating to dissolve the material.)

Dr. Ottoboni advised that the composition of Zhou appears to be supersaturated because crystals fall out of solution after 4 or 5 days.

The Examiner noted that Zhou [0012] and [0013] appear to indicate a particle size of 50 - 150 nm. Dr. Ottoboni advised that this is a starting point for an injectable composition per USP (United States Pharmacopeia) and that this appears to refer to the size of the lipid droplet in Zhou. Dr. Ottoboni noted that with aprepitant, the crystals form on the outside of the lipid droplets. (Photographs were filed as drawings for this case, but it is hard to see fine details on the photographs.) The Examiner noted that Zhou teaches that aprepitant is not soluble in water or organic solvent. [0017]

The Examiner asked if Applicant tried something like Ex. 4 of the spec. using Applicant's method as opposed to Zhou's. Dr. Ottoboni directed the Examiner to Ex. 5 of the spec., which uses oleic acid instead of oleate and which also uses the lower amount of emulsifier as per Zhou. Ex. 5 of the spec. is prepared using the method Applicant uses for examples according to their claimed invention. The Examiner noted the lower ratio of emulsifier to drug in Ex. 4 and 5 when compared to the other examples. Per Dr. Ottoboni, this is an important feature of their invention.

Dr. Ottoboni noted that Zhou uses a typical drug lipid solution where one optimizes the amount of oil. In comparison, Applicant found that the amount of emulsifier vs. drug is more important for this drug.

As Dr. Ottoboni explained the chemistry behind the invention: Aprepitant is a NK1 inhibitor. It contains fluorocarbon with florinated phenyl groups, which are hydrophobic. Aprepitant also has amine and amide groups, as well as oxygens, which are hydrophilic. Therefore aprepitant is kind-of a "hydrid" compound. It is neither hydrophobic nor hydrophilic; parts of the molecular are hydrophobic while other parts are hydrophilic. Aprepitant was found to be best solubilized in the emulsifier, rather than in aqueous phase or oil phase. So optimizing the amount of emulsifer vs. drug content is important.

The Examiner advised that Applicant's arguments and evidence appear to show criticality of the claimed range for the emulsifier and criticality of the ratio of aprepitant to emulsifier. Unless the Examiner finds 102 art, the Examiner believes this evidence and arguments will over come most 103 rejections. The Examiner will need to conduct a follow up search and therefore cannot promise that the claims are allowable at this point.

Review Article

Neurokinin-1 receptor antagonists for chemotherapy-induced nausea and vomiting

Fahad Aziz

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Abstract: Chemotherapy can be a life-prolonging treatment for many cancer patients, but it is often associated with profound nausea and vomiting that is so distressing that patients may delay or decline treatment to avoid these side effects. The discovery of several NK1 receptor antagonists is a big revolution to dealt this problem.

NK1 receptor antagonists prevent both acute and delayed chemotherapy-induced nausea and vomiting (CINV).

These agents act centrally at NK-1 receptors in vomiting centers within the central nervous system to block their activation by substance P released as an unwanted consequence of chemotherapy. By controlling nausea and vomiting, these agents help improve patients' daily living and their ability to complete multiple cycles of chemotherapy. They are effective for both moderately and highly emetogenic chemotherapy regimens. Their use might be associated with increased infection rates; however, additional appraisal of specific data from RCTs is needed.

Key Words: Chemotherapy; chemotherapy-induced nausea and vomiting; NK1 receptor

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Introduction

Nausea and vomiting are common and feared symptoms among cancer patients (1-3), and up to 80% of patients will experience chemotherapy-induced nausea and vomiting (CINV) without prophylactic therapy (1-5). Nausea and vomiting can lead to deteriorated nutritional status, compromise adherence to therapy, and impair quality of life irrespective of etiology. Furthermore, inadequate emesis control may lead to anticipatory nausea and vomiting, which is a challenging clinical condition to treat and potentially refractory to standard medications (6-7).

The intrinsic risk of the chemotherapy regimen is the main risk factor for the overall degree of CINV and can vary depending on the class of drug, dose, schedule, and route of administration used. The current classification of the risk of emesis is mostly based on the intrinsic emetogenic potential of the chemotherapy regimen (8-10) which is stratified as follows: high emetogenic potential (>90% risk of inducing vomiting after chemotherapy administration), moderate emetogenic potential (>30-90% risk), low emetogenic potential (10-30% risk), and minimal emetogenic potential (<10% risk) (8).

Patient characteristics such as young age, female sex, low alcohol intake, poor performance status, previous history of bowel obstruction, history of motion sickness, and experience of emesis during pregnancy (11-13) may further increase the emetic risk but are currently not factors that are integrated into the choice of optimal prophylactic therapy. Additionally, disease-related features such as the primary site of the cancer, the histological subtype, clinical stage, presence of brain metastases, and presence of end organ dysfunction may further impact the probability of emesis. The use of adjunct therapies such opioid-

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derivatives, radiotherapy, or other medications can also exacerbate symptoms. Although the stratification usually applied to evaluate emetic risk does not consider important and relevant clinical and disease factors, it is accepted worldwide.

Cisplatin is the main example of a drug with a high emetogenic potential; doses greater than 50-mg/m^2 lead to nausea and vomiting in more than 90% of patients if no prophylactic therapy is used (8). Other drugs with high emetogenic potential include cyclohosphamide (>1,500 mg/m^2), carmustine (>250 mg/m^2), and dacarbazine.

Efforts to prevent and treat CINV have been usually directed at blocking neurotransmitter receptors in the area postrema, which is a chemoreceptor trigger site for vomiting in response to emetic drugs. Dopamine, endorphin, serotonin, and neurokinin receptors are found in this area and are targets for preventing and treating CINV (14). Although the combination of dexamethasone and serotonin (5-HT3) receptor antagonists remained the backbone of CINV prevention until recently, this combination has been reported to lack effectiveness in preventing late onset CINV (15-20).

More than a decade ago, Navari *et al.* showed that neurokinin-1 receptor (NK1R) antagonists improve CINV when used in combination with cisplatin-based chemotherapy (21). These antagonists prevent the binding of substance P to the NK1R. Unopposed, substance P, a tachykinin family neuropeptide that functions as a neurotransmitter and neuromodulator, can mediate the induction of vomiting pathways by binding to the NK1R (22).

Current guidelines for CINV management (11,13,23) strongly recommend the use of NK1R antagonists for CINV prophylaxis in the acute and delayed phases for highly emetogenic chemotherapy schedules.

This review evaluates the overall effectiveness and safety of NK1R antagonists in the prevention of CINV (24).

History of the development

The substance P story has been nearly 80 years in the telling from the isolation of the peptide, to it's sequencing, to the cloning of its receptor and the synthesis of the first small molecule antagonists.

The journey began in 1931 when a pharmacologically active substance was isolated from the brain and intestine and named substance P—"P" for powder—by the pioneering pharmacologist John Gaddum working with Ulf von Euler (25). In 1954, Gaddum continued his research into this extract and showed that substance P was concentrated in the emetic centers of the brain, commenting in his manuscript in the Journal of Physiology that "it is tempting to speculate why this is so" (26).

It was not until 40 years later, in 1971, that the active substance, an 11-amino acid peptide, was isolated, sequenced, and synthesized de novo by Susan Lehman and her group (27,28). Yet another 20 years went by, to 1991, before the receptor for substance P, the NK-1 receptor, was identified and cloned (29), and small-molecule blockers or antagonists of substance P that could access these NK-1 receptors in the emetic centers in the brain were developed. Amazingly, in line with Gaddum's speculation, these substance P antagonists (SPAs) were shown to be the broadest spectrum antiemetics ever described.

Research at Merck began during the 1980s to discover SPAs with which to understand the role of substance P in health and disease. For many years this proved a difficult task, and only peptide antagonists that were unsuitable, as oral drug candidates and that did not cross the blood-brain barrier were synthesized.

In the early 1990s, the first small molecule brain-penetrant SPAs became available (30), enabling the investigation of the therapeutic potential of the NK-1 antagonist mechanism. Despite strong anatomical evidence supporting a potential role for substance P in pain and affective disorders, the SPAs were inactive as analgesics and as antidepressants. The hypothesis that substance P was involved in emesis was initially supported by three preclinical observations: substance P was localized in the emetic centers of the brain, substance P could cause emesis, and depletion of substance P using a toxin (resiniferatoxin) could prevent emesis in preclinical species with a vomiting reflex. The critical proof that the substance P/NK-1 receptor axis played a crucial role in mediating the vomiting response to a number of stimuli came with demonstration that highly selective SPAs had profound activity against emesis induced by broad range of central and peripherally acting emetogens (30,31). Moreover, these SPAs were active in multiple species with a vomiting reflex against a broad range of emetogens (32), giving high confidence that the mechanism would translate to clinically meaningful activity (33). In particular, SPAs were active against emesis induced by chemotherapeutic agents such as cisplatin and uniquely against the delayed phase of emesis that can recur days after treatment with such cytotoxic agents (34).

Continued research into the antiemetic mechanism of action of the SPAs showed that SPA molecules had to

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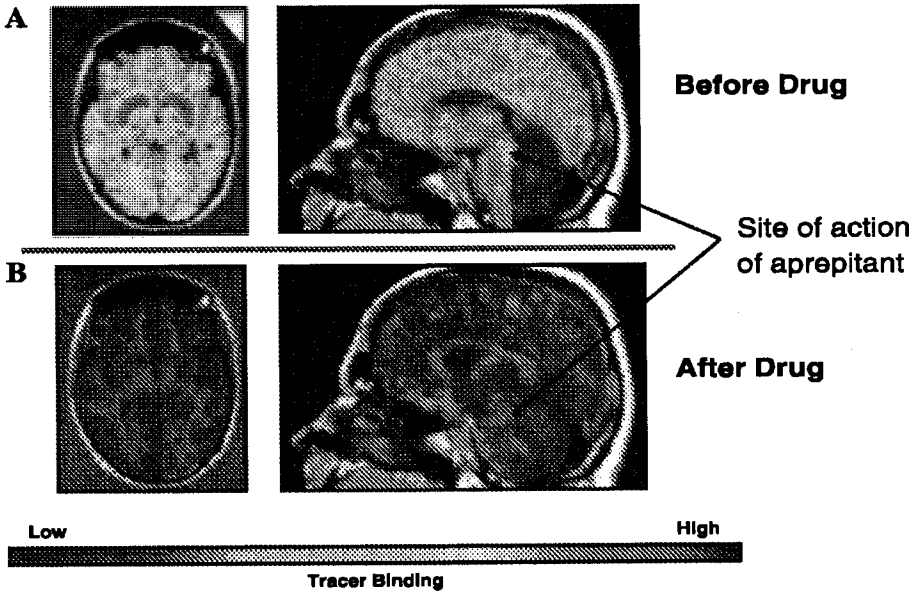


Figure 1 Occupancy of central NK-1receptors by aprepitant visualized using PET imaging

penetrate the brain to access central NK-1 receptors in the brain-stem emetic centers in order to be effective in preclinical models. Potent SPAs that did not cross into the brain were ineffective as antiemetics (35).

PET imaging of NK1-receptors in brain

Confirmation that drugs reach their targets using markers of engagement is key to successful proof- of-concept testing, especially for drugs acting in the brain. Knowing how hard and how long a drug must hit its target to produce the desired pharmacologic effect is important for dose selection and clinical trial design and interpretation.

A novel PET tracer that imaged NK-1 receptors in living human brain was developed to visualize the central sites of action of NK1-antagonist and to assess their occupancy by therapeutic doses of the drug (*Figure 1*). Understanding the relationships between dose, plasma concentration, and receptor occupancy for NK1 antagonist helped establish the link between target engagement and changes in the CINV clinical endpoint. This knowledge was important in the selection of the dosing regime for the regulatory filing these agents and ensured that the lowest drug exposure that achieved target engagement consistent with >90% blockade of NK-1 receptors was chosen, thereby maximizing the potential therapeutic safety window (36,37).

NK1 receptors antagonist: leraning about the biology of chemotherpay induced nausea

The development of multiple NK1 Receptors antagonists provided new insights into the pharmacological and pathophysiological mechanisms involved in emesis.

Both peripheral (glosophararyngeal and vagal nerves) and central (cortical and cerebellar) pathways can activate neuronal nuclei in the brainstem and trigger a sequence of events that results in the vomiting reflex. The 5-HT3 receptor antagonists are thought to exert their actions predominantly on the peripheral terminals of vagal afferents in the gastrointestinal tract and in the chemoreceptor trigger zone (CRTZ) that lays in the area postrema outside of the blood-brain barrier to block the activating effects of serotonin released during chemotherapy. The CRTZ signals to another area, the nucleus tractus solitarius (NTS), in the brain stem that also receives emetogenic stimuli from higher brain centers (e.g., cortical and vestibular) as well as gastrointestinal vagal afferents, and is thought to define the patterns of central activity underlying CINV.

Preclinical studies suggest that it is here within the NTS that NK1 receptors antagonists exert their strongest

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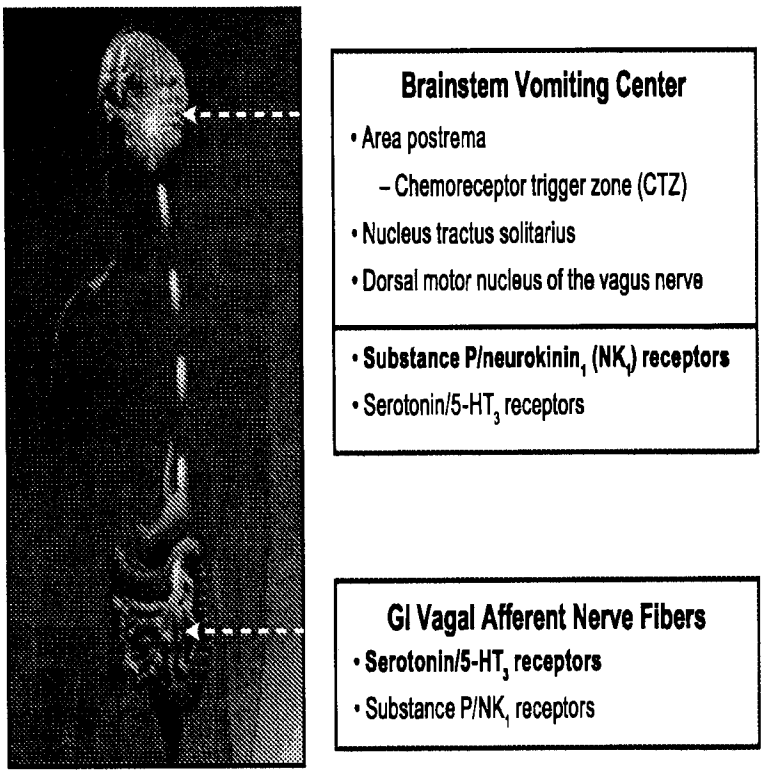


Figure 2 Sites of action of 5-HT3 and NK-1 receptor antagonists

antiemetic properties through central inhibition of the emesis pattern generator. This central site of action is the likely explanation for the unique broad antiemetic pharmacological profile of these agents, indicating that substance P acting at central NK-1 receptors is one of the final common mechanisms involved in activation and coordination of the vomiting reflex (38).

The acute and delayed clinical time course of CINV has previously been linked to serotonin release and inflammation by the clinical effectiveness of 5-HT3 antagonists and steroids, respectively. The discovery of the NK 1 receptor antagonists and clinical experience with these agents has furthered our understanding and provided substantial evidence for involvement of substance P throughout the CINV response.

The prolonged efficacy profile of many of these agents, including the delayed phase, indicates that substance P acting at central NK-1 receptors becomes increasingly important with time in the pathophysiology of the overall CINV response (39).

These observations support the clinical rationale for combination therapy with 5-HT3 receptor antagonists (e.g., ondansetron), steroids (e.g., dexamethasone), and NK1 receptors antagonists to optimize control of CINV (*Figure 2*).

NK1 receptors antagonists and interactions with chemo-based agents

NK1R antagonists are known to increase the bioavailability of dexamethasone, and this pharmacokinetic interaction could potentially play a role in the higher incidence of infection among patients who have been treated with NK1R antagonists. The Chawla *et al.* study (40) did not decrease the day 1 dexamethasone dose in the NK1R arm, whereas the Schmoll *et al.* (41) and Poli-Bigelli *et al.* (42) studies did. Nevertheless, it seems unlikely that increased dexamethasone bioavailability could have any impact on the infection rates because these three trials presented similar findings.

NK1R antagonists can also increase the bioavailability

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of chemotherapy agents metabolized by cytochrome P450 3A4 (CYP3A4), such as etoposide, taxanes, irinotecan, vinca alkaloids, anthracyclines, and cyclophosphamide. Two of three studies suggested that adverse events could be more common among patients receiving an NK1R antagonist plus a CYP3A4-metabolized chemotherapy (43).

Current and future challenges

Ongoing discovery and development efforts in the program aim to identify simplified dose regimens of these newly made NK 1 receptors agents.

In August 2010, a single-dose formulation of fosaprepitant (NK 1 Receptor antagonist) for IV administration was approved in the European Union for use instead of the 3-day oral regimen of aprepitant (another NK 1 receptor antagonist), together with a 5-HT3 receptor antagonist and a corticosteroid.

Additionally, in November 2010, the FDA approved a single-dose formulation, EMEND for Injection 150 mg, for patients receiving highly emetic chemotherapy. This new regimen provides a more simple treatment to patients who will not need to worry about taking capsules of EMEND on days two and three, ensuring compliance with therapy and improving convenience for both patients and healthcare professionals.

The incidence of cancer in pediatric patients is still a concern despite the availability of treatments for the different tumors and the resilience of the patients. There are no clear guidelines for antiemetic therapy in pediatric cancer patients since the available scientific data are very limited; this allows pediatric cancer patients to go through their chemotherapy treatment with suboptimal therapy for prevention of CINV. An age-appropriate formulation of these agents (powder for suspension) is currently under research and development to extend its benefits to pediatric patients.

NK1 receptors antagonists and infections

However, the increased risk of severe infection is probably not explained by hematological toxicity because leukopenia, neutropenia, severe neutropenia, and febrile neutropenia were not increased by the addition of NK1R antagonists.

NK1R is known to have a role in neurogenic response to injury, and its suppression might impair natural defenses against infection (44-46) that might predispose patients to a greater risk of infection through immune-mediated mechanisms that are poorly understood.

Conclusions

In conclusion, NK1R antagonists improved control of CINV in the acute, delayed, and overall phases for patients who received highly and moderately emetogenic chemotherapy. CINV control in the acute phase seemed to be a surrogate for CINV control in the delayed phase. The use of NK1R antagonists may be associated with a statistically significantly increased risk of severe infection. A more comprehensive evaluation of the safety profile of NK1R antagonists and additional appraisal of specific data from RCTs is needed.

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References

1. Laszlo J, Lucas VS Jr. Emesis as a critical problem in chemotherapy. N Engl J Med 1981;305:948-9.
2. Morran C, Smith DC, Anderson DA, et al. Incidence of nausea and vomiting with cytotoxic chemotherapy: a prospective randomised trial of antiemetics. Br Med J 1979;1:1323-4.
3. Teunissen SC, Wesker W, Kruitwagen C, et al. Symptom prevalence in patients with incurable cancer: a systematic review. J Pain Symptom Manage 2007;34:94-104.
4. Griffin AM, Butow PN, Coates AS, et al. On the receiving end. V: patient perceptions of the side effects of cancer chemotherapy in 1993. Ann Oncol 1996;7:189-95.
5. Osoba D, Zee B, Warr D, et al. Quality of life studies in chemotherapy-induced emesis. Oncology 1996;53:92-5.
6. Wilcox PM, Fetting JH, Nettesheim KM, et al. Anticipatory vomiting in women receiving cyclophosphamide, methotrexate, and 5-FU (CMF) adjuvant chemotherapy for breast carcinoma. Cancer Treat Rep 1982;66:1601-4.
7. Morrow GR, Lindke J, Black PM. Predicting development of anticipatory nausea in cancer patients: prospective examination of eight clinical characteristics. J Pain Symptom Manage 1991;6:215-23.
8. Hesketh PJ, Kris MG, Grunberg SM, et al. Proposal for classifying the acute emetogenicity of cancer chemotherapy. J Clin Oncol 1997;15:103-9.
9. Gralla RJ, Osoba D, Kris MG, et al. Recommendations for the use of antiemetics: evidence-based, clinical practice

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guidelines. American Society of Clinical Oncology. J Clin Oncol 1999;17:2971-94.
10. Prevention of chemotherapy- and radiotherapy-induced emesis: results of Perugia Consensus Conference. Antiemetic Subcommittee of the Multinational Association of Supportive Care in Cancer (MASCC). Ann Oncol 1998;9:811-9.
11. American Society of Clinical Oncology, Kris MG, Hesketh PJ, et al. American Society of Clinical Oncology guideline for antiemetics in oncology: update 2006. J Clin Oncol 2006;24:2932-47.
12. Roila F, Donati D, Tamberi S, et al. Delayed emesis: incidence, pattern, prognostic factors and optimal treatment. Support Care Cancer 2002;10:88-95.
13. NCCN. NCCN Clinical Practice Guidelines in Oncology: Antiemesis Version 1. 2012. Fort Washington, PA: NCCN, 2011.
14. Borison HL, McCarthy LE. Neuropharmacology of chemotherapy-induced emesis. Drugs 1983;25:8-17.
15. Jantunen IT, Kataja VV, Muhonen TT. An overview of randomised studies comparing 5-HT3 receptor antagonists to conventional anti-emetics in the prophylaxis of acute chemotherapy-induced vomiting. Eur J Cancer 1997;33:66-74.
16. Smith DB, Newlands ES, Rustin GJ, et al. Comparison of ondansetron and ondansetron plus dexamethasone as antiemetic prophylaxis during cisplatin-containing chemotherapy. Lancet 1991;338:487-90.
17. Roila F, Tonato M, Cognetti F, et al. Prevention of cisplatin-induced emesis: a double-blind multicenter randomized crossover study comparing ondansetron and ondansetron plus dexamethasone. J Clin Oncol 1991;9:675-8.
18. Hesketh PJ, Harvey WH, Harker WG, et al. A randomized, double-blind comparison of intravenous ondansetron alone and in combination with intravenous dexamethasone in the prevention of high-dose cisplatin-induced emesis. J Clin Oncol 1994;12:596-600.
19. Hesketh P. Management of cisplatin-induced delayed emesis. Oncology 1996;53:73-7.
20. Roila F, Bracarda S, Tonato M, et al. Ondansetron (GR38032) in the prophylaxis of acute and delayed cisplatin-induced emesis. Clin Oncol (R Coll Radiol) 1990;2:268-72.
21. Navari RM, Reinhardt RR, Gralla RJ, et al. Reduction of cisplatin-induced emesis by a selective neurokinin-1-receptor antagonist. L-754,030 Antiemetic Trials Group. N Engl J Med 1999;340:190-5.
22. Saito R, Takano Y, Kamiya HO. Roles of substance P and NK(1) receptor in the brainstem in the development of emesis. J Pharmacol Sci 2003;91:87-94.
23. Herrstedt J, Roila F, ESMO Guidelines Working Group. Chemotherapy-induced nausea and vomiting: ESMO clinical recommendations for prophylaxis. Ann Oncol 2008;19:ii110-2.
24. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6:e1000097.
25. V Euler US, Gaddum JH. An unidentified depressor substance in certain tissue extracts. J Physiol 1931;72:74-87.
26. Amin AH, Crawford TB, Gaddum JH. The distribution of substance P and 5-hydroxytryptamine in the central nervous system of the dog. J Physiol 1954;126:596-618.
27. Chang MM, Leeman SE, Niall HD. Amino acid sequence of substance P. Nat New Biol 1971;232: 86-7.
28. Tregear GW, Niall HD, Potts JT Jr, et al. Synthesis of substance P. Nat New Biol 1971;232: 879.
29. Fong TM, Anderson SA, Yu H, et al. Differential activation of intracellular effector by two isoforms of human neurokinin-1 receptor. Mol Pharmacol 1992;41:24-30.
30. Snider RM, Constantine JW, Lowe JA 3rd, et al. A potent nonpeptide antagonist of the substance P (NK1) receptor. Science 1991;251:435-7.
31. Bountra C, Bunce K, Dale T, et al. Anti-emetic profile of a non-peptide neurokinin NK1 receptor antagonist, CP-99,994, in ferrets. Eur J Pharmacol 1993;249:R3-4.
32. Tattersall FD, Rycroft W, Hargreaves RJ, et al. The tachykinin NK1 receptor antagonist CP-99,994 attenuates cisplatin induced emesis in the ferret. Eur J Pharmacol 1993;250:R5-6.
33. Watson JW, Gonsalves SF, Fossa AA, et al. The anti-emetic effects of CP-99,994 in the ferret and the dog: role of the NK1 receptor. Br J Pharmacol 1995;115:84-94.
34. Andrews PLR, Rudd JA. The role of tachykinins and the tachykinin NK1 receptor in nausea and emesis. In: Holzer P. eds. Handbook of Experimental Pharmacology. New York: Springer, 2004:359-440.
35. Tattersall FD, Rycroft W, Cumberbatch M, et al. The novel NK1 receptor antagonist MK-0869 (L-754, 030) and its water soluble phosphoryl prodrug, L-758,298, inhibit acute and delayed cisplatin-induced emesis in ferrets. Neuropharmacology 2000;39:652-63.
36. Frank R, Hargreaves R. Clinical biomarkers in drug discovery and development. Nat Rev Drug Discov 2003;2:566-80.
37. Bergström M, Hargreaves RJ, Burns HD, et al. Human positron emission tomography studies of brain neurokinin 1 receptor occupancy by aprepitant. Biol Psychiatry 2004;55:1007-12.
38. Hornby PJ. Central neurocircuitry associated with emesis.

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Am J Med 2001;111:106S-112S.
39. Hesketh PJ, Van Belle S, Aapro M, et al. Differential involvement of neurotransmitters through the time course of cisplatin-induced emesis as revealed by therapy with specific receptor antagonists. Eur J Cancer 2003;39:1074-80.
40. Chawla SP, Grunberg SM, Gralla RJ, et al. Establishing the dose of the oral NK1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting. Cancer 2003;97:2290-300.
41. Schmoll HJ, Aapro MS, Poli-Bigelli S, et al. Comparison of an aprepitant regimen with a multiple-day ondansetron regimen, both with dexamethasone, for antiemetic efficacy in high-dose cisplatin treatment. Ann Oncol 2006;17:1000-6.
42. Poli-Bigelli S, Rodrigues-Pereira J, Carides AD, et al. Addition of the neurokinin 1 receptor antagonist aprepitant to standard antiemetic therapy improves control of chemotherapy-induced nausea and vomiting. Results from a randomized, double-blind, placebo-controlled trial in Latin America. Cancer 2003;97:3090-8.
43. Grunberg SM, Rolski J, Strausz J, et al. Efficacy and safety of casopitant mesylate, a neurokinin 1 (NK1)-receptor antagonist, in prevention of chemotherapy-induced nausea and vomiting in patients receiving cisplatin-based highly emetogenic chemotherapy: a randomised, double-blind, placebo-controlled trial. Lancet Oncol 2009;10:549-58.
44. Beer S, Weighardt H, Emmanuilidis K, et al. Systemic neuropeptide levels as predictive indicators for lethal outcome in patients with postoperative sepsis. Crit Care Med 2002;30:1794-8.
45. Chavolla-Calderón M, Bayer MK, Fontán JJ. Bone marrow transplantation reveals an essential synergy between neuronal and hemopoietic cell neurokinin production in pulmonary inflammation. J Clin Invest 2003;111:973-80.
46. Verdrengh M, Tarkowski A. The impact of substance P signalling on the development of experimental staphylococcal sepsis and arthritis. Scand J Immunol 2008;67:253-9.

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Aprepitant

A Review of its Use in the Prevention of Chemotherapy-Induced Nausea and Vomiting

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Data Selection

Sources: Medical literature published in any language since 1980 on aprepitant, identified using Medline and EMBASE, supplemented by AdisBase (a proprietary database of Adis International). Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: Medline search terms were 'aprepitant' or 'L-754030' or MK-0869' or 'MK-869'. EMBASE search terms were 'aprepitant' or 'L-754030' or 'MK-0869' or 'MK-869'. AdisBase search terms were 'aprepitant' or 'MK-0869' or 'MK-869'. Searches were last updated 15 February 2004.

Selection: Studies in patients treated with highly emetogenic chemotherapy who received aprepitant. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: Aprepitant, chemotherapy-induced nausea and vomiting, pharmacodynamics, pharmacokinetics, therapeutic use, tolerability.

Contents

Summary 778
1. Chemotherapy-Induced Nausea and Vomiting (CINV) 781
2. Pharmacodynamic Properties 782
3. Pharmacokinetic Properties 782
   3.1 Absorption and Distribution 783
   3.2 Metabolism and Elimination 783
   3.3 Drug Interactions 783
4. Efficacy in the Prevention of CINV 784
   4.1 Complete Response 786
   4.2 Other Endpoints 787
      4.2.1 Impact on Daily Living 788
5. Tolerability 788
6. Dosage and Administration 790
7. Place of Aprepitant in the Prevention of CINV 791

Summary

Abstract

Aprepitant (Emend®) is the first commercially available drug from a new class of agents, the neurokinin NK_1 receptor antagonists. Oral aprepitant, in combination with other agents, is indicated for the prevention of acute and delayed chemotherapy-induced nausea and vomiting (CINV) associated with highly emetogenic chemotherapy in adults.

In three randomised, double-blind, placebo-controlled trials comparing aprepitant (125mg day 1, 80mg once daily on days 2 and 3 or 2–5) plus standard therapy (intravenous ondansetron and oral dexamethasone) with standard therapy plus placebo, overall complete responses (primary endpoint, defined as no emesis and no rescue therapy) were seen in significantly more patients in the aprepitant arms (63–73% versus 43–52%, $p < 0.01$ for all comparisons).

Complete responses and complete protection during the acute and delayed phase, and overall complete protection were also observed in significantly more patients in the aprepitant arms. The difference between treatment groups was more marked in the overall and delayed phases than in the acute phase.

The antiemetic efficacy of aprepitant plus standard therapy in the prevention of CINV was maintained for up to six cycles of chemotherapy.

Where assessed, more patients in the aprepitant plus standard therapy arms than the standard therapy plus placebo arms reported no impact of CINV on daily life, as assessed by the Functional Living Index-Emesis.

Aprepitant is generally well tolerated. The most common adverse events in randomised trials were asthenia or fatigue. Other adverse events experienced by aprepitant recipients include anorexia, constipation, diarrhoea, nausea (after day 5 of the study) and hiccups. In addition to being a substrate for cytochrome P450 (CYP) 3A4, aprepitant is also a moderate inhibitor and inducer of this isoenzyme as well as an inducer of CYP2C9. Thus, aprepitant has the potential to interact with other agents metabolised by hepatic CYP isoenzymes. In one trial, there was a higher incidence of serious infection or febrile neutropenia in the aprepitant plus standard therapy arm than the standard therapy plus placebo arm; this was attributed to a pharmacokinetic interaction between aprepitant and dexamethasone. In subsequent trials, a modified dexamethasone regimen was used.

In conclusion, when added to standard therapy (a serotonin $5\text{-}HT_3$ receptor antagonist and a corticosteroid), aprepitant is effective and generally well tolerated in the prevention of CINV associated with highly emetogenic chemotherapy in adults. Despite marked advances in the prevention of CINV, standard therapy does not protect all patients. The addition of aprepitant to standard therapy provides an advance in the prevention of both acute and delayed CINV in adults with cancer.

Pharmacodynamic Properties

Aprepitant is a selective high-affinity neurokinin NK_1 receptor antagonist which crosses the blood-brain barrier in humans. Aprepitant competitively binds the NK_1 receptors in the brain, thereby blocking the effects of substance P (the natural ligand) in the CNS. The drug has little or no affinity for other neurokinin receptors, rabbit L-type calcium channels, or the receptors targeted by other agents for chemotherapy-induced nausea and vomiting (CINV). In ferrets receiving cisplatin, aprepitant has shown acute- and delayed-phase antiemetic activity and augmented the antiemetic effects of ondansetron and dexamethasone.

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Pharmacokinetic Properties

The pharmacokinetics of aprepitant are non-linear across the recommended dose range (recommended regimen 125mg on day 1, 80mg on days 2 and 3). Following this dosage, the area under the concentration-time curve, maximum plasma concentration (C_{max}) and time to reach C_{max}, respectively, were 19.6 μg • h/mL, 1.6 μg/mL and ≈4 hours on day 1 and 21.2 μg • h/mL, 1.4 μg/mL and ≈4 hours on day 3.

Aprepitant is extensively metabolised in the liver. Based on *in vitro* data using human liver microsomes, aprepitant is metabolised mainly by cytochrome P450 (CYP) 3A4, and to a lesser extent by CYP1A2 and CYP2C19.

The apparent plasma clearance and apparent terminal elimination half-life ranged from 62 to 90 mL/min and 9 to 13 hours.

Aprepitant does not have clinically relevant effects on the pharmacokinetics of the serotonin 5-HT_3 receptor antagonists ondansetron and granisetron. It is unlikely to interact with substrates for the p-glycoprotein transporter.

Aprepitant is a substrate for, and a moderate inhibitor and inducer of, CYP3A4; it is also an inducer of CYP2C9. Coadministration of aprepitant can increase the plasma concentration of CYP3A4 substrates and decrease the plasma concentration of CYP2C9 substrates. Concomitant administration of aprepitant with CYP3A4 inhibitors may increase the plasma concentrations of aprepitant, while concurrent administration with drugs that strongly induce CYP3A4 activity may reduce the plasma aprepitant concentration.

Therapeutic Efficacy

In three multicentre, randomised, double-blind, placebo-controlled trials in adults, aprepitant (125mg day 1, 80mg days 2 and 3 or 2–5) plus standard therapy (intravenous ondansetron and oral dexamethasone) showed efficacy superior to that of standard therapy plus placebo for the primary endpoint, overall complete response (defined as no emesis and no rescue therapy during 0–120 hours post-cisplatin, 63–73% versus 43–52%, $p < 0.01$). Complete responses were also significantly higher with aprepitant plus standard therapy than standard therapy plus placebo during both the acute (83–89% versus 68–78%) and delayed phases (68–75% versus 45–56%).

Complete protection (no emesis, no rescue therapy and no significant nausea) during the overall, acute and delayed phases was observed in significantly more patients in the aprepitant plus standard therapy arms than the standard therapy plus placebo arms (overall 56–65% versus 40–49%, acute 79–85% versus 65–75%, delayed 61–67% versus 41–52%). For both complete response and complete protection, the difference between the treatment arms was numerically greater in the overall and delayed phases than the acute phase.

A greater proportion of patients in the aprepitant plus standard therapy arms than in the standard therapy plus placebo arms reported no emetic episodes (overall, acute and delayed, regardless of rescue therapy, $p < 0.01$). In a phase II study, significantly more patients in the aprepitant arm reported no overall or delayed phase significant nausea ($p < 0.01$); in the acute phase there was no difference between the treatment groups. In two phase III trials, there was no significant difference between the two treatment arms for overall and delayed phase significant nausea. In these trials, however, significantly more patients in the aprepitant plus standard therapy arms did not require rescue medication ($p < 0.05$).

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The antiemetic efficacy of aprepitant plus standard therapy was maintained for up to six cycles of chemotherapy. In a pooled analysis of two phase III trials, the proportion of patients with no emesis and no significant nausea in the aprepitant plus standard therapy arms was significantly greater than that in the standard therapy plus placebo arms in each treatment cycle ($p \leq 0.006$).

In three trials, more aprepitant plus standard therapy recipients than standard therapy plus placebo recipients reported no impact of CINV on daily life, as assessed by the Functional Living Index-Emesis.

Tolerability

In randomised, double-blind trials in adults, aprepitant plus standard therapy was generally well tolerated. Unless stated otherwise, statistical analyses were not reported for tolerability data. The most common adverse event for patients receiving aprepitant plus standard therapy was asthenia/fatigue, which occurred in 17.2–20% of aprepitant plus standard therapy recipients and 9.5–17% of standard therapy plus placebo recipients. Other adverse events occurring in ≥10% of patients in the aprepitant arms were anorexia, constipation, diarrhoea, nausea (after day 5 of the study) and hiccups.

In a dose-finding phase II trial, the incidence of drug-related adverse events in patients receiving aprepitant (125mg day 1, 80mg subsequent days) plus standard therapy was not significantly different to that for those receiving standard therapy plus placebo (27 versus 26%). In two phase III trials, 19.5 and 14.0% of patients in the aprepitant plus standard therapy arms compared with 14.4 and 13.5% in the standard therapy plus placebo arms experienced a drug-related adverse event.

The proportions of patients with a documented serious adverse event were numerically similar in the aprepitant plus standard therapy arms and the standard therapy plus placebo arms of the phase III trials (11.0 versus 9.8% and 16.1 versus 17.0%). In the phase II trial, significantly more patients in the aprepitant plus standard therapy arm than in the standard therapy plus placebo arm experienced serious adverse events (21.5 versus 12.3%, relative risk 1.74, $p = 0.032$); this difference was attributed to a numerically higher incidence of serious infections or febrile neutropenia in the aprepitant plus standard therapy group. The higher rate of infections in the aprepitant plus standard therapy group was assumed to be because of elevated plasma dexamethasone concentrations, as a result of a pharmacokinetic interaction with aprepitant. In subsequent phase III trials, the dexamethasone regimen was modified and no difference was observed in the incidence of serious infections between treatment arms.

In the three trials, 7.1, 8.0 and 2% of patients in the aprepitant plus standard therapy arms discontinued treatment because of an adverse event, compared with 5.3, 5.3 and 1% in the standard therapy plus placebo arms.

Dosage and Administration

Aprepitant (oral, in combination with a corticosteroid and a serotonin 5-HT_3 receptor antagonist) is approved in the US for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy in adults. Aprepitant is not approved for use in children or adolescents. The recommended aprepitant dosage is 125mg administered 1 hour prior to initiating chemotherapy treatment (day 1) and 80mg once daily on days 2 and 3.

Concomitant administration of aprepitant with drugs that are CYP3A4 substrates or inhibitors should be approached with caution because these drugs may

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interact with aprepitant. Doses of coadministered corticosteroids should be reduced. Coadministration of strong CYP3A4 inducers may decrease the efficacy of aprepitant.

While being treated with aprepitant, patients receiving oral contraceptives should use alternative or back-up contraception and those on long-term warfarin therapy should have their clotting status monitored.

Aprepitant has not been evaluated for longer than 5 days per cycle or for the treatment of established emesis and nausea in patients receiving emetogenic chemotherapy.

1. Chemotherapy-Induced Nausea and Vomiting (CINV)

Nausea and vomiting are two of the most distressing adverse effects associated with chemotherapy.[1] Poorly controlled chemotherapy-induced nausea and vomiting (CINV) can lead to dehydration, malnutrition and electrolyte imbalance, and can cause physical damage, including Mallory-Weiss tears of the oesophagus.[1,2] These symptoms can result in treatment delays, or a patient may refuse to continue treatment.[2] CINV can also have an economic impact on the management of patients with cancer, including increased hospitalisation and nursing costs.[1,2]

There are three types of CINV: anticipatory, acute and delayed.[1] Anticipatory CINV is also referred to as conditioned or psychological CINV and occurs before a cycle of chemotherapy, it is usually seen in patients who have previously experienced CINV.[1,3] Acute CINV is usually defined as occurring within 24 hours after chemotherapy.[1] Traditionally, delayed CINV has been defined as that occurring more than 24 hours after chemotherapy. However, recent evidence suggests that it may start as early as 16 hours after chemotherapy.[4] Delayed CINV may persist for up to 7 days.[1] Delayed CINV is not as well understood as acute CINV and is more difficult to treat.[2]

Several variables predict the risk of emesis.[1] The principal indicators of the probability of emesis are the chemotherapeutic agents used; for example, cisplatin (>50 mg/m^2) induces nausea and vomiting in >90% of patients not receiving antiemetic prophylaxis.[2] The degree of emetic risk is also influenced by patient characteristics.[1] For example, the risk of emesis is higher in females, younger patients and individuals who had poor control with past chemotherapy. In addition, low alcohol intake history, low social functioning and high fatigue scores are factors associated with a higher risk of emesis. Poor control of acute CINV is the main risk factor for the development of delayed CINV.[1]

Although there have been marked advances in recent years, the physiological mechanism of CINV is complex and still incompletely understood.[2] The chemoreceptor trigger zone (CTZ), which is located in the area postrema on the floor of the fourth ventricle and sends impulses to the vomiting centre, is thought to play an important role in chemotherapy-induced emesis.[4] Several receptors have been identified in the CTZ and research has focused on dopamine, serotonin and neurokinin receptors.[1,5]

Serotonin is an important mediator of symptoms for acute CINV.[4] The development of serotonin 5-HT$_3$ receptor antagonists has vastly improved antiemetic therapy.[1] Guidelines from a number of societies in the US and Europe recommend administering a 5-HT$_3$ receptor antagonist and a corticosteroid to prevent acute CINV in patients receiving highly emetogenic chemotherapy agents.[4,6-8] For the prevention of delayed CINV in patients receiving cisplatin, guidelines recommend a corticosteroid with either a 5-HT$_3$ receptor antagonist or metoclopramide (a dopamine D$_2$ receptor antagonist).

Despite improvements in antiemetic therapy, a number of patients receiving highly emetogenic chemotherapy still experience CINV, particularly delayed CINV.[9] It appears that serotonin is not the

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main mediator of delayed emesis (see section 7).[4] Recent research suggests that substance P, a tachykinin which acts through the neurokinin NK_1 receptor pathways, may also be involved in delayed CINV.[1]

Aprepitant (Emend®)[1] [figure 1] is the first commercially available drug from a new class of agents, the NK_1 receptor antagonists.[10] The NK_1 receptor antagonists are being investigated for the treatment of depression, migraine, pain and emesis.[11] This review focuses on the use of aprepitant in the prevention of CINV in adults with cancer receiving highly emetogenic chemotherapy regimens.

2. Pharmacodynamic Properties

Aprepitant antagonises the effects of substance P by binding to NK_1 receptors.[12] Substance P, the most abundant neurokinin in the CNS of mammals,[13] has been implicated in the pathophysiology of many conditions including asthma, pain, migraine, schizophrenia, anxiety and emesis, particularly chemotherapy-induced delayed emesis.[14] Aprepitant competitively binds to the NK_1 receptors in the brain, thereby blocking the effects of substance P (the natural ligand) in the CNS.[15,16]

In order to have an acute antiemetic effect, NK_1 receptor antagonists must be able to enter the CNS.[15] In human and animal studies, aprepitant crossed the blood-brain barrier and occupied NK_1 receptors in the brain (data from US prescribing information[17]). Aprepitant exhibits a high affinity and is selective for human NK_1 receptors expressed in Chinese hamster ovary (CHO) cells. In two studies, aprepitant, at concentrations of 0.10[18] and 0.09 nmol/L,[19] displaced 50% of suhstance P from NK_1 receptors. In contrast, aprepitant has a low affinity for human NK_2 and NK_3 receptors and rabbit L-type calcium channels. High concentrations of aprepitant were required to displace 50% of neurokinin A from NK_2 receptors (4.5[18] and >1 μmol/L[19]), neurokinin B[18] or eledoisin[19] from NK_3 receptors (300[18] and >100 nmol/L[19]) and diltiazem from the L-type calcium channel in rabbit skeletal muscle (8000[18] and >1000 nmol/L[19]). Aprepitant also has little or no affinity for the receptors targeted by other agents for CINV (5-HT_3, dopamine and corticosteroid receptors).[17]

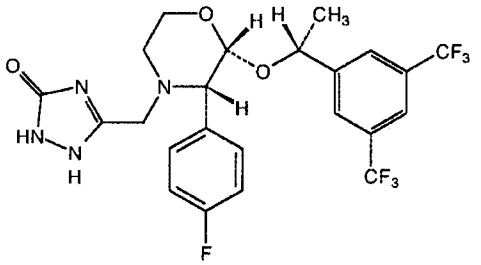


Fig. 1. Chemical structure of aprepitant.

Both oral and intravenous formulations of aprepitant have shown acute- and delayed-phase antiemetic activity in ferrets receiving cisplatin.[18-20] In ferrets receiving cisplatin, the antiemetic effects of aprepitant plus either ondansetron or dexamethasone were greater than those observed when ondansetron or dexamethasone were administered alone.[18]

3. Pharmacokinetic Properties

Unless stated otherwise, data in this section are from the US prescribing information for aprepitant and refer to oral administration of the drug.[17] The pharmacokinetics of aprepitant have been studied in healthy volunteers and in patients with renal or hepatic impairment. There have been no formal pharmacokinetic studies conducted in paediatric patients. Although the pharmacokinetics of aprepitant are altered by gender, age (study compared adults aged ≥65 years with those aged <65 years) and race (study compared Hispanic, White and Black adults), these changes (≤31%) are not considered clinically relevant and no dosage adjustment is necessary. When compared with those in healthy volunteers, there were no clinically relevant differences in the pharmacokinetics of aprepitant in patients with mild-to-moderate hepatic insufficiency or severe renal insufficiency or in those requiring haemodialysis; there are no data on the pharmacokinetic pro-

1 The use of trade names is for product identification purposes only and does not imply endorsement.

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file of aprepitant in patients with severe hepatic insufficiency (see section 6).[17]

3.1 Absorption and Distribution

Across the recommended dose range (80 or 125 mg/day; see section 6), the pharmacokinetics of aprepitant are nonlinear.[17] The difference in the area under the concentration-time curve (AUC) for single 80 and 125mg doses was 26% greater than dose proportional. Following the recommended aprepitant dosage regimen (125mg on day 1, 80 mg/day on days 2 and 3), the AUC and maximum plasma concentration (C_{max}) were 19.6 μg • h/mL and 1.6 μg/mL on day 1 and 21.2 μg • h/mL and 1.4 μg/mL on day 3. The time to reach C_{max} was ≈4 hours on each day. The bioavailability of aprepitant (mean absolute oral bioavailability ≈60–65%) is not appreciably affected by food.[17]

The total protein binding and mean steady-state apparent volume of distribution for aprepitant are >95% and ≈70L.[17] In rats and rabbits, aprepitant crosses the placenta.

3.2 Metabolism and Elimination

Aprepitant is metabolised extensively in the liver.[17] Based on *in vitro* data using human liver microsomes, aprepitant is metabolised mainly by cytochrome P450 (CYP) 3A4, and to a lesser extent by CYP1A2 and CYP2C19. CYP2D6, CYP2C9 and CYP2E1 were not involved in aprepitant metabolism. Up to 72 hours after healthy young adults received a single oral dose of [^{14}C]-aprepitant 300mg, ≈24% of the radioactivity in the plasma was present as unchanged drug, indicating the presence of metabolites. In human plasma, seven weakly active metabolites of aprepitant have been identified.[17]

Aprepitant is eliminated mainly as metabolites. The apparent plasma clearance (CL) and apparent terminal elimination half-life ($t_{1/2}$) of aprepitant ranged from 62 to 90 mL/min and 9 to 13 hours (dosage, administration route and patient type not reported).[17] When healthy volunteers received a single intravenous dose of labelled aprepitant prodrug (dose not stated), the radioactivity was recovered in urine (57%) and faeces (45%) [oral administration not studied].[17]

3.3 Drug Interactions

Aprepitant does not have clinically relevant effects on the pharmacokinetics of the 5-HT_3 receptor antagonists ondansetron and granisetron;[23] no pharmacokinetic studies with dolasetron or palonosetron have been published.[17] Aprepitant had no effects on the pharmacokinetics of digoxin, leading the investigators to conclude that aprepitant is unlikely to interact with substrates for the p-glycoprotein transporter.[24]

Aprepitant is a substrate for, and a moderate inhibitor and inducer of, CYP3A4, as well as an inducer of CYP2C9 (see section 6).[17] Coadministration of aprepitant with CYP2C9 substrates may result in lower plasma concentrations of the latter drugs (table I). As an inhibitor of CYP3A4, if aprepitant is coadministered with agents metabolised by CYP3A4 isoenzymes, plasma concentrations of these drugs may increase. When aprepitant was administered with the CYP3A4 substrates dexamethasone, methylprednisolone and midazolam, the systemic exposure to these drugs increased (table I). In clinical trials, aprepitant was frequently administered with etoposide, vinorelbine or paclitaxel, which are metabolised by CYP3A4 (section 5). The CYP3A4 substrates docetaxel, vinblastine, vincristine and ifosfamide were received by small numbers of patients in clinical trials.[17] Because aprepitant is also an inducer of CYP3A4, the concentration of intravenously administered CYP3A4 substrates may decrease if they are coadministered with aprepitant (UK product information, coadministered drugs not specified).[25] Aprepitant has not been studied for its inductive effect on oral CYP3A4 substrates.

Concomitant administration of aprepitant with CYP3A4 inhibitors may increase the plasma concentrations of aprepitant, while administration with drugs that strongly induce CYP3A4 activity may reduce the aprepitant plasma concentration (table I).[17] Although the pharmacokinetics of both aprepitant and diltiazem (a moderate CYP3A4 inhibitor) were affected when the two agents were coadmin-

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Table I. Pharmacokinetic drug interactions with oral aprepitant (APP). Studies are not included if there were no effects or if the effects were described as not clinically relevant

Study[a]	Coadministered drug	Regimen (day 1/subsequent days) [mg/day]	Effects on pharmacokinetics	Comments or recommendations[b]
Effects of APP on the pharmacokinetics of coadministered drugs				
Majumdar et al.[21]	MID (sensitive CYP3A4 substrate)	Oral MID 2/2,[c] APP 125/80[d]	MID AUC ↑ 2.3-fold day 1, 3.3-fold day 5, $p < 0.01$	Consider effects of increased plasma concentrations of MID and other benzodiazepines metabolised via CYP3A4 (alprazolam, triazolam) when coadministering with APP
McCrea et al.[22]	MET (CYP3A4 substrate)	MET IV125/PO40,[e] APP 125/80[e]	MET AUC ↑ 1.34- and 2.46-fold on days 1 and 3, $p < 0.01$	Reduce IV MET by ≈25%, reduce PO MET by ≈50%
McCrea et al.[22]	DEX (CYP3A4 substrate)	Oral DEX 20/8,[d] APP 125/80[d]	DEX AUC ↑ ≈2.2-fold, days 1 and 5, $p < 0.01$	Reduce dose of DEX;[22] in clinical trials with APP DEX dose was reduced to 12/8
US prescribing information[17]	WAF [S(−) WAF is a CYP2C9 substrate]	Long-term WAF therapy, APP 125/80[e]	5 days after final APP dose S(−) WAF C_{min} ↓ 34%, prothrombin time ↓ 14%[f]	Monitor prothrombin time for 2 weeks (particularly at 7–10 days) following initiation of APP therapy
US prescribing information[17]	TOL (CYP2C9 substrate)	Oral TOL 500/500,[g] APP 125/80[e]	TOL AUC ↓ 23% day 4, 28% day 8, 15% day 15[f]	No recommendations documented
US prescribing information[17]	Ethinyl estradiol/ norethindrone	Oral ethinyl estradiol 0.035, norethindrone 1, APP 100 for 14 days	Ethinyl estradiol and norethindrone AUC ↓ by 43 and 8%[f]	Efficacy of oral contraceptives may be reduced, alternative/back-up contraception required
Effects of coadministered agents on the pharmacokinetics of APP				
US prescribing information[17]	KET (strong CYP3A4 inhibitor)	KET 400 for 10 days, APP 125 day 5	APP AUC and $t_{1/2}$ ↑ ≈5- and ≈3-fold[f]	Caution required in coadministration of APP with strong CYP3A4 inhibitors
US prescribing information[17]	RIF (strong CYP3A4 inducer)	RIF 600 for 14 days, APP 375 day 9	APP AUC and $t_{1/2}$ ↓ ≈11- and ≈3-fold[f]	APP plasma concentrations and efficacy may be reduced by coadministration of drugs that induce CYP3A4 activity
Effects on pharmacokinetics of both drugs				
US prescribing information[17]	PAR	PAR 20, APP 85 or 170[h]	Both drugs AUC and C_{max} ↓ ≈25% and ≈20%[f]	No recommendations documented

a All studies were reported in the US prescribing information.[17]

b Recommendations are from the US prescribing information.[17]

c Subsequent day = day 5.

d Subsequent days = days 2–5.

e Subsequent days = days 2, 3.

f Statistical analysis not reported.

g Subsequent days = days 4, 8, 15.

h Both drugs were administered once daily, treatment length not specified.

AUC = area under the concentration-time curve; **C_{max}** = peak plasma concentration; **C_{min}** = minimum plasma concentration; **CYP** = cytochrome P450; **IV** = intravenous; **KET** = ketaconazole; **MET** = methylprednisolone; **MID** = midazolam; **PAR** = paroxetine; **PO** = oral; **RIF** = rifampicin; **$t_{1/2}$** = terminal elimination half-life; **TOL** = tolbutamide; **WAF** = warfarin; ↓ indicates decreased; ↑ indicates increased.

istered, these changes were not considered clinically relevant.[17]

4. Efficacy in the Prevention of CINV

The efficacy of oral aprepitant in combination with standard regimens of oral dexamethasone and intravenous ondansetron has been investigated in several trials in adult patients with cancer receiving high-dose cisplatin-based chemotherapy.[17,26-32] The fact that NK_1 receptor antagonists are being investigated in combination with other antiemetics, rather than as monotherapy, may be explained by the results of a small (n = 53) randomised, double-blind trial comparing an intravenous prodrug of aprepitant

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(L-758,298) with ondansetron.[33] In this trial, ondansetron was numerically superior in the prevention of acute emesis, while L-758,298 was significantly superior in the prevention of delayed emesis ($p = 0.005$), suggesting that the two classes of drugs may be useful as combination therapy.

This section focuses on three multicentre (sites both in and outside the US), randomised, double-blind, placebo-controlled trials.[26-28,32] Key endpoints and efficacy data for these trials are reviewed in table II and table III. All of these trials are fully published; one is a phase II dose-finding study[26,27] and two are phase III studies.[28,32]

Patients received aprepitant (125mg on day 1 administered 1 hour prior to cisplatin infusion, and 80mg once daily on days 2 and 3[28,32] or days 2–5[26,27]) plus standard therapy. Standard therapy consisted of intravenous ondansetron and dexamethasone (see table III for details of regimen and dosages). The three trials compared aprepitant plus standard therapy with standard therapy plus placebo.[26-28,32] Based on pharmacokinetic interaction data (section 3.3), the standard dexamethasone dose was reduced in the aprepitant arms of the phase III trials.[28,32]

In the phase II dose-ranging study,[26,27] the original patient allocation schedule was changed after the first 202 patients. Efficacy data relating to the original schedule[27] and the second schedule ($n = 381$)[26] have been reported separately. The focus of the paper reporting the data from the original schedule was the sustainability of the aprepitant efficacy for up to six cycles of chemotherapy.[27] A companion study[34] to the dose-finding trial[26] assessed the impact of nausea and vomiting on daily life; this study has been published in full and is discussed in section 4.2.1.

In the three trials, eligible patients were at least 18 years of age with solid tumours confirmed by histology and a Karnofsky score ≥60.[26-28,32] Patients were cisplatin naive at the beginning of the trials. The cisplatin dosage was >50 mg/m^2 in the phase III study by Hesketh et al.,[32] and ≥70 mg/m^2 in the other trials.[26-28] The mean cisplatin dose was ≈80 mg/m^2.[26-28,32] The US prescribing information[17] states that in the phase III trials, concomitant chemotherapeutic agents in addition to cisplatin were administered to 95% of aprepitant recipients. The most common agents were etoposide (19% of patients), fluorouracil (18%), gemcitabine (16%), vinorelbine (15%), paclitaxel (9%), cyclophosphamide (9%), doxorubicin (7%) and docetaxel (2%).[17]

Exclusion criteria included the following: abnormal laboratory values;[26-28,32] uncontrolled disease or active infection that would compromise patient safety;[26-28,32] a planned multiple-day, cisplatin-based chemotherapy regimen in a single cycle;[26-28,32] moderately or highly emetogenic chemotherapy on the days prior to or after cisplatin;[26,28] radiation therapy to the abdomen or pelvis within 1 week before the first day of the study,[26-28,32] or between day 1 and day 6;[28,32] treatment with a nonapproved drug within 4 weeks of study entry;[26,27] and CNS malignancy.[26,27] Additional antiemetic agents were not permitted (except

Table II. Efficacy endpoints for randomised, double-blind trials of aprepitant with ondansetron and dexamethasone in patients receiving cisplatin-based chemotherapy

Endpoint	Definition/assessment
Primary	
Overall complete response[26-28,32]	No emesis and no rescue therapy, 0–120h post-cisplatin
Secondary or exploratory	
Delayed or acute phase complete response[26,28,32]	Complete response 0–24h (acute) or 24–120h post-cisplatin
No emesis[26,28,32]	No emetic episodes, regardless of use of rescue therapy
No nausea[26,28,32]	VAS of <5mm where 0mm is 'no nausea' and 100mm is 'nausea as bad as it could be'
No significant nausea[26,28,32]	VAS <25mm
Complete protection[26,28,32]	No emesis, no rescue therapy and no significant nausea
Total control[26,28,32]	No emesis, no rescue therapy and no nausea
No rescue therapy[26,28,32]	
No impact of CINV on daily life (NIDL)[28,32]	FLIE score of 6 on a 7-point scale

CINV = chemotherapy-induced nausea and vomiting; **FLIE** = Functional Living Index-Emesis; **h** = hours; **VAS** = visual analogue scale.

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Table III. Efficacy of oral aprepitant (APP) in adult patients (pts) receiving cisplatin-based chemotherapy.[a] Data are from the first treatment cycle of multicentre, randomised, double-blind, placebo-controlled trials. Pts received APP plus standard therapy or standard therapy plus placebo. The APP dosage was 125mg on day 1 and 80mg on subsequent days unless otherwise specified. Standard therapy was ondansetron (OND) plus dexamethasone (DEX). Intravenous OND 32mg was given on day 1 in all treatment arms of all trials. The DEX (oral) dosage was 20mg on day 1 and 8mg on subsequent days unless otherwise specified

Study	Antiemetic treatment		Complete response (% of pts)[b]			Complete protection (% of pts)		
	DEX regimen	APP or PL regimen (no. of pts)[c]	overall[d]	acute	delayed	overall	acute	delayed
Chawla et al.[26][e]	DEX[f]	APP[f] (134)	71**	83*	73**	65**	79*	67**
	DEX[f]	APP[g] (120)	59*	76	64**	54*	72	58**
	DEX[f]	PL[f] [127]	44	71	45	40	67	41
de Wit et al.[27][e]	DEX[f]	APP[f] (81)	64*[h]	NR	NR	NR	NR	NR
	DEX[f]	PL[f] (86)	49[h]	NR	NR	NR	NR	NR
Hesketh et al.[32]	DEX[i]	APP[i] (260)	73***	89***	75***	63**	85**	66**
	DEX[k]	PL (260)	52	78	56	49	75	52
Poli-Bigelli et al.[28]	DEX[i]	APP[i] (261)	63**	83**	68**	56**	80**	61**
	DEX[k]	PL (263)	43	68	47	41	65	44

a Cisplatin ≥70[26-28] or >50 mg/m2.[32]

b See table II for definitions of endpoints.

c Intention-to-treat population[26] or modified intention-to-treat population (patients who received cisplatin and the study drug and had at least one post-treatment efficacy evaluation).[28,32]

d Overall complete response was the primary endpoint.

e The original patient allocation schedule was changed after the first 202 patients. Efficacy data relating to the original schedule[27] and the second schedule (n = 381)[26] have been reported separately.

f Subsequent days = days 2–5.

g 40mg on day 1 and 25 mg/day on days 2–5.

h Complete response rates were estimated using a transitional probability approach; reported rates were 0.64 for the APP plus standard therapy arm vs 0.49 for the standard therapy plus PL arm.[32]

i 12mg on day 1 and 8 mg/day on days 2–4.

j Subsequent days = days 2 and 3.

k 20mg on day 1 and 16 mg/day on days 2–4.

NR = not reported; **PL** = placebo; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs standard therapy plus PL.

as rescue therapy for established nausea and vomiting) within 72 hours of day 1 in one trial,[26,27] or 2 days prior to day 1 and between day 1 and 6 in the other two studies.[28,32] Corticosteroid therapy was permitted in the phase II dose-finding study,[26,27] provided it was not administered within 72 hours of day 1.

In all trials the primary endpoint was overall complete response (see table II for definitions of primary and secondary endpoints).[26-28,32] When endpoints were split by phase, the acute and delayed phases were defined as 0–24 hours and 25–120 hours post-cisplatin (overall: 0–120 hours). Analyses were based on the intention-to-treat population[26,27] or modified intention-to-treat population (patients who received cisplatin, study drug and had at least one post-treatment efficacy evaluation).[28,32] Efficacy results reported in this section are for the first cycle of therapy and an aprepitant dosage of 120mg on day 1 and 80mg on subsequent days, unless stated otherwise.

4.1 Complete Response

Overall complete responses (primary endpoint) were observed in significantly more patients in the aprepitant plus standard therapy arms compared with the standard therapy plus placebo arms (63–73% versus 43–52%; $p < 0.01$ for all comparisons; table III).[26-28,32] Complete responses during the acute and delayed phases were also significantly higher in the aprepitant plus standard therapy arms than the standard therapy plus placebo arms (table

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III).[26,28,32] The difference between the treatment arms was more marked in the overall and delayed phases than the acute phase.[26,28,32] Acute phase complete responses were observed in 83–89% of patients in the aprepitant plus standard therapy arms compared with 68–78% in the standard therapy plus placebo arms.[26,28,32] Respective delayed phase complete responses ranged from 68–75% compared with 45–56%.[26,28,32]

Complete response rates with aprepitant plus standard therapy were maintained across up to six cycles of chemotherapy, whereas they declined over subsequent cycles with standard therapy plus placebo (between-cycle statistical analysis not performed).[27] Across cycles 1–6, complete response was observed in higher percentages of patients receiving aprepitant plus standard therapy than in those receiving standard therapy plus placebo. Between-treatment differences reached statistical significance in cycle 1 (64 versus 49%; $p < 0.05$ by logistic regression analysis) and cycles 5 and 6 (59 versus 34% in both cycles; $p < 0.05$ using bootstrap method).[27] Caution must be exercised in interpreting these results, however, because by cycle 6 there were only 11 patients in the aprepitant plus standard therapy arm and seven patients in the standard therapy plus placebo arm.

4.2 Other Endpoints

Overall, acute phase and delayed phase complete protection was observed in significantly more patients in the aprepitant plus standard therapy arms compared with the standard therapy plus placebo arms (overall 56–65% versus 40–49%, acute 79–85% versus 65–75%, delayed 61–67% versus 41–52%, $p < 0.05$ for all comparisons, table III).[26,28,32]

Significantly more aprepitant plus standard therapy recipients than standard therapy plus placebo recipients reported no emetic episodes regardless of rescue therapy in the overall, acute and delayed phases ($p < 0.01$, figure 2).[26,28,32] The proportions

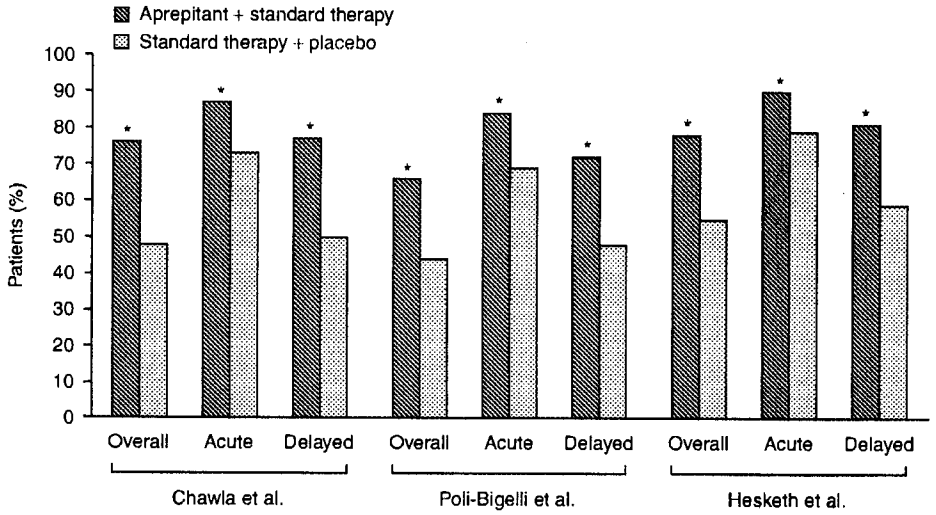


Fig. 2. Efficacy of oral aprepitant in combination with intravenous ondansetron and oral dexamethasone in adult patients receiving one cycle of cisplatin-based chemotherapy: proportions of patients experiencing no emetic events (regardless of rescue therapy).[26,28,32] Data are from three multicentre, randomised, double-blind trials. In the trial by Chawla et al.,[26] all patients received ondansetron (32mg) and dexamethasone (20mg) on day 1 of chemotherapy and dexamethasone (8mg) on days 2–5 (standard therapy) and either aprepitant 125mg on day 1 and 80 mg/day on days 2–5 (n = 134), or placebo on days 1–5 (n = 127). In the trials by Poli-Bigelli et al.[28] (n = 523) and Hesketh et al.[32] (n = 521) patients received either aprepitant (125mg), ondansetron (32mg) and dexamethasone (12mg) on day 1, followed by aprepitant (80mg, days 2 and 3) and dexamethasone (8 mg/day, days 2–4) or ondansetron (32mg) and dexamethasone (20mg) on day 1 followed by dexamethasone 8mg twice daily on days 2–4 (standard therapy) plus placebo. Analyses were based on the intention-to-treat population[26] or modified intention-to-treat population (patients who received cisplatin and the study drug and had at least one post-treatment efficacy evaluation).[28,32] * $p < 0.01$ vs standard therapy plus placebo.

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of patients in the aprepitant plus standard therapy arms with no overall, acute phase and delayed phase emesis regardless of rescue therapy ranged from 66–78%, 84–90% and 72–81%, respectively. As with complete response and complete protection, the difference between the two arms was more marked for the overall and delayed phase than the acute phase. In the dose-finding phase II study,[26] significantly more patients in the aprepitant plus standard therapy group than in the standard therapy plus placebo group reported no significant overall or delayed nausea (81.7 versus 58.7%; 83.3 versus 62.7%, both $p < 0.01$); there was no significant difference in the acute phase. In the phase III trials, there was no significant difference between the two treatment arms for overall and delayed phase significant nausea (analysis of acute phase nausea was performed in only one study[32] in which there were no marked between-treatment differences [statistical analysis not performed]).[28,32] However, at each phase in these trials significantly more aprepitant plus standard therapy recipients than standard therapy plus placebo recipients did not require rescue medication ($p < 0.05$).[28,32]

The correlation between the control of acute vomiting and the incidence of delayed vomiting was examined using pooled data from the phase III trials (data available as an abstract[35]). Of the patients who did not experience acute vomiting, 374 of 451 (83%) in the aprepitant plus standard therapy arms and 260 of 387 (67%) in the standard therapy plus placebo arms did not experience delayed vomiting. Of the patients who did have acute vomiting, 22 of 69 (32%) and 20 of 136 (15%) had no delayed vomiting. The authors concluded that, because adding aprepitant to standard therapy decreased delayed vomiting by a similar magnitude in patients who did experience acute vomiting (17%) and those who did not (16%), aprepitant had a pharmacological effect on delayed vomiting, not simply a 'carry-over' effect from prevention of acute vomiting.[35]

The antiemetic efficacy of aprepitant plus standard therapy was maintained for up to six cycles of chemotherapy (reported in a pooled analysis of the phase III trials[36]). The proportion of patients experiencing no emesis and no significant nausea in the aprepitant plus standard therapy arms was significantly greater in each cycle than that in the standard therapy plus placebo arms (61 [n = 516] versus 46% [n = 522] in cycle 1 and 59 [n = 89] versus 40% [n = 78] in cycle 6, $p \leq 0.006$).[36]

Higher doses of aprepitant in combination with dexamethasone,[31] dexamethasone and granisetron,[29,31] or dexamethasone and an intravenous prodrug of aprepitant (L-758,298)[30] have also shown antiemetic efficacy in patients receiving cisplatin-based chemotherapy.

4.2.1 Impact on Daily Living

More aprepitant plus standard therapy recipients experienced no impact of CINV on daily living than standard therapy plus placebo recipients.[28,32,34] In the phase III trials[28,32] and the companion to the study by Chawla et al.,[34] patients completed the Functional Living Index-Emesis (FLIE) as an assessment of the impact of CINV on daily life. In the companion study,[34] an average score of 6 on a 7-point scale indicated no impact on daily life. A significantly higher proportion of patients receiving aprepitant plus standard therapy compared with those receiving standard therapy plus placebo reported that CINV had no impact on daily life (106 of 126 patients [84%] versus 79 of 119 [66%], $p < 0.01$).[34] In the phase III trials,[28,32] a total FLIE score of >108 indicated little or no impact of nausea and vomiting on patients' daily lives. In a pooled analysis of the two trials, 78% of male aprepitant plus standard therapy recipients scored >108, compared with 67% of male standard therapy plus placebo recipients ($p < 0.001$). Respective proportions for female patients were 69 and 60% ($p < 0.05$) [results from an abstract[37]].

5. Tolerability

This section focuses on three trials in adult patients using an aprepitant dosage regimen of 125mg on day 1 and 80 mg/day on days 2 and 3 or 2–5, which is similar to the recommended regimen. Tolerability results have been published in full for all three trials;[26,28,32] the US prescribing information reports a pooled analysis of tolerability data from

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the two phase III trials.[17] The phase II dose-finding trial[26] included patients from both the original and the second allocation schedule in the tolerability analysis (see section 4 for trial design of the phase III and II trials). In these trials, aprepitant plus standard therapy (ondansetron and dexamethasone) was compared with standard therapy plus placebo (see section 4.1 for further details).[26,28,32] Adverse events were recorded up to 14 days post-treatment.[26,28,32] Drug-related adverse events were described as those considered to be possibly, probably or definitely related to the study drug.[26,28,32] In the phase II dose-finding trial,[26] statistical analyses were performed for overall events, but not for individual events. Unless stated otherwise, no other statistical analyses were reported.

Aprepitant plus standard therapy was generally well tolerated. Asthenia/fatigue was the most common adverse event for patients receiving aprepitant therapy, and occurred in a numerically higher proportion of patients in the aprepitant plus standard therapy arms compared with the standard therapy plus placebo arms (17.2 versus 9.5%;[32] 18.4 versus 14.0%;[28] 20 versus 17%[26]) [see figure 3 for adverse events in the pooled analysis]. Other adverse events occurring in ≥10% of patients in the aprepitant arms were as follows: anorexia, constipation, diarrhoea, nausea and hiccups (nausea and vomiting were considered as adverse events only after day 5 of the study or if they were serious, led to discontinuation or considered to be drug-related).[26,28,32]

The proportions of patients who discontinued treatment because of an adverse event were 7.1,[28] 8.0[32] and 2%[26] in the aprepitant plus standard therapy arms, compared with 5.3,[28] 5.3[32] and 1%[26] in the standard therapy plus placebo arms (reasons for discontinuation were not specified). There was no significant difference between the two arms for discontinuations because of serious adverse events in the phase II trial (relative risk [RR] 1.32, p = 0.804).[26]

In this trial,[26] the incidence of drug-related adverse events for patients receiving aprepitant plus standard therapy was not significantly different from that for patients receiving standard therapy plus placebo (27 versus 26%). In the two phase III trials,[28,32] drug-related adverse events were experienced by 19.5[28] and 14.0%[32] of aprepitant plus standard therapy recipients compared with 14.4[28] and 13.5%[32] of those receiving standard therapy plus placebo.

The proportion of patients experiencing serious adverse events was similar across both treatment arms in the trials reported by Poli-Bigelli et al.[28] and Hesketh et al.[32] (11.0 versus 9.8% and 16.1 versus 17.0%). In each trial, only one serious event in the aprepitant plus standard therapy arm was considered to be drug related (disorientation in one patient in one trial,[28] perforating duodenal ulcer considered to be related to dexamethasone in the

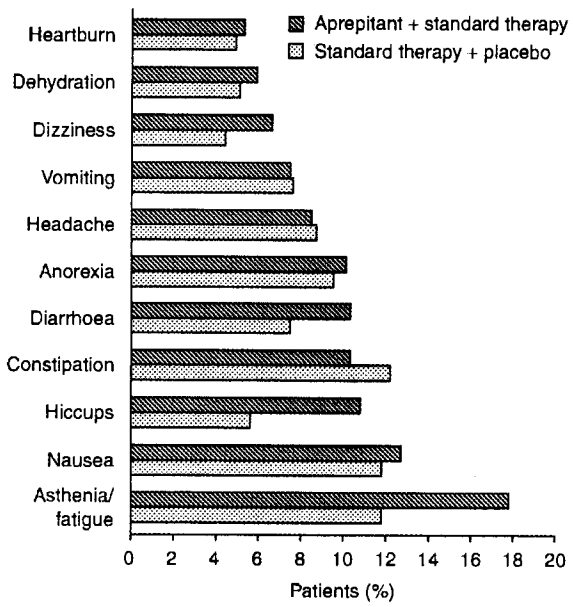


Fig. 3. Adverse events with oral aprepitant plus standard therapy in patients receiving cisplatin-based chemotherapy.[17] Data are from a pooled analysis of data from the first treatment cycle of two phase III, multicentre, randomised, double-blind trials.[28,32] Events occurring in ≥5% of patients in either treatment arm are shown. Patients (n = 1094) received aprepitant (125mg on day 1 and 80mg once daily on days 2 and 3) plus standard therapy (intravenous ondansetron 32mg on day 1 and oral dexamethasone 12mg on day 1 and 8mg on day 2 and 3) or standard therapy (intravenous ondansetron 32mg on day 1 and oral dexamethasone 20mg on day 1 and 8mg twice daily on day 2 and 3) plus placebo. Statistical analysis was not reported. Nausea and vomiting were considered adverse events only after day 5 of the study, or at any time if they were serious, resulted in discontinuation or considered to be drug related.[28,32]

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other trial[32]). However, in the phase II trial,[26] a significantly higher proportion of patients who received the aprepitant plus standard therapy regimen experienced serious adverse events, compared with those who received standard therapy plus placebo (21.5 versus 12.3%, RR 1.75, p = 0.032). The difference between the two arms was attributed to a numerically higher incidence of serious infections or febrile neutropenia in the aprepitant plus standard therapy group (13 versus 4.2%).[26] The investigators suggested that this increased incidence may have been because aprepitant increases the systemic exposure to dexamethasone; high-dose corticosteroids have been associated with increased susceptibility to infection.[26] In the aprepitant arms of the two phase III trials, in which the standard dexamethasone regimen was modified, there was no difference between the aprepitant plus standard therapy groups and the standard therapy plus placebo groups in the incidence of serious infections.[28,32]

There were no serious drug-related laboratory adverse events, and no patients died or discontinued treatment because of drug-related laboratory events.[26,28,32] In the aprepitant plus standard therapy arms 5.7,[28] 2.3[32] and 8%[26] of patients experienced a drug-related laboratory event, compared with 3.9,[28] 1.2[32] and 9%[26] of patients receiving standard therapy plus placebo. In the pooled analysis, the most common laboratory adverse events for patients receiving aprepitant plus standard therapy were as follows: proteinuria (6.8%) and increases in levels of alanine aminotransferase (6.0%), aspartate aminotransferase (3.0%), blood urea nitrogen (4.7%) and serum creatinine (3.7%).[17] Increases in aminotransferase levels were usually mild and transient.

In each arm of one of the phase III trials, 164 patients received CYP3A4-metabolised agents (including etoposide, vinca alkaloids and taxanes) as part of their chemotherapy regimen (see section 3 for metabolism and drug interaction details).[28] In this subgroup, the proportion of patients experiencing serious adverse events was greater in the aprepitant plus standard therapy arm than in the standard therapy plus placebo arm (15.9 versus 8.5%, statistical analysis not reported). In patients who did not receive CYP3A4-metabolised agents, the incidence of serious adverse events was higher in the standard therapy plus placebo arm (11.6 versus 4.2%). In contrast, in the other phase III trial, it was stated that for patients who received CYP3A4-metabolised agents, the incidence of serious adverse events was similar in both treatment arms.[32] In this trial, 100 patients in the aprepitant plus standard therapy group and 85 in the standard therapy plus placebo group received CYP3A4-metabolised agents.

6. Dosage and Administration

Oral aprepitant, in combination with a corticosteroid and a 5-HT_3 receptor antagonist, is approved in the US for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy in adults.[17] The recommended aprepitant dosage is 125mg administered 1 hour prior to initiating chemotherapy treatment (day 1) and 80mg in the morning of days 2 and 3. Long-term continuous use of aprepitant has not been studied and is therefore not recommended.[17] Aprepitant has not been evaluated in the treatment of patients with established nausea and vomiting.[16]

Caution should be exercised in administering aprepitant concomitantly with drugs that are CYP3A4 substrates or inhibitors (see section 3.3 for drug interaction information).[17] Aprepitant should not be used with pimozide, terfenadine, astemizole or cisapride because inhibition of CYP3A4 by aprepitant may result in elevated plasma concentrations of these agents and potentially cause serious reactions. Concomitant corticosteroid dosages should be adjusted; oral dexamethasone and methylprednisolone doses should be reduced by ≈50%, intravenous methylprednisolone dose should be reduced by ≈25%. The efficacy of aprepitant may be decreased by coadministration with drugs that strongly induce CYP3A4 activity.[17]

Patients receiving oral contraceptives should use back-up or alternative contraception while they are receiving aprepitant.[17] In the 2 weeks following initiation of the 3-day course of aprepitant, patients

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receiving warfarin should have their clotting status closely monitored, particularly at 7–10 days.[17]

The safety and efficacy of aprepitant has not been established in paediatric or adolescent patients.[16,17] The administration of aprepitant to patients with severe hepatic insufficiency (Child-Pugh score >9) has not been studied, therefore, caution is required in administering the drug to this patient group. No dosage adjustment is needed in patients with mild to moderate hepatic insufficiency (Child-Pugh score 5–9).[17] No dosage adjustment is necessary in patients with renal insufficiency. The safety of aprepitant in pregnant women has not been established. The drug should only be taken during pregnancy if it is considered clearly necessary. Breast feeding is not recommended during aprepitant therapy.[17]

7. Place of Aprepitant in the Prevention of CINV

Guidelines from a number of societies in the US and Europe recommend that all patients receiving moderately or highly emetogenic chemotherapy agents are given antiemetic therapy to manage acute and delayed CINV.[4,6-8,38,39] The goal in these patients is prevention, rather than cure, because once present, CINV is very difficult to treat.[40]

The discovery that serotonin was involved in the mediation of CINV and the subsequent development of 5-HT_3 receptor antagonists was an advance in the prevention of CINV.[5] These agents are generally well tolerated, and provide improved control of acute emesis compared with previously available agents (e.g. metoclopramide-based therapy).[41] Because poor control of acute CINV is the main risk factor for the development of delayed CINV, 5-HT_3 receptor antagonists also have an influence on the control of delayed events.[42] Where studied, the 5-HT_3 receptor antagonists have similar efficacy and tolerability to each other when recommended dosages are used for the prevention of CINV with highly emetogenic chemotherapy regimens.[5,43] Several 5-HT_3 receptor antagonists are available as both oral and intravenous formulations and show similar efficacy for both routes.[1] Although the oral preparations are generally used, there are situations in which the intravenous route is preferable.[4]

However, the 5-HT_3 receptor antagonists are not effective in the prevention of CINV in all patients,[5] and there is conflicting evidence regarding the benefits of continuing treatment with these agents beyond day 1.[1,39] The low levels of serotonin metabolites in urine at 48 hours compared with 6 hours after the initiation of chemotherapy, together with the clinical evidence indicating that 5-HT_3 receptor antagonists are less effective in delayed than acute CINV, suggest that serotonin is not the main mediator of delayed CINV.[4]

Corticosteroids exhibit efficacy in the prevention of CINV during both the acute and, when continued for several days, delayed phase.[1] The exact mechanism of action of these agents is as yet unclear, but their antiemetic activity may be due to their effect on mediators of inflammation.[1] Short-term corticosteroid therapy is generally well tolerated and does not seem to cause clinically relevant immunosuppression.[1] In numerous trials, the addition of a corticosteroid to a 5-HT_3 receptor antagonist has improved the prevention of acute CINV compared with a 5-HT_3 receptor antagonist alone (reviewed by Gralla et al.[7]).

Several antiemetic agents are antagonists of D_2 receptors.[7] The most commonly used of these agents is metoclopramide, a substituted benzamide. At high doses, metoclopramide also acts as a serotonin receptor antagonist.[5] Although metoclopramide has lower efficacy than 5-HT_3 receptor antagonists for the prevention of acute CINV,[44] when added to a corticosteroid it is as effective as a 5-HT_3 receptor antagonist plus a corticosteroid for the prevention of delayed CINV.[5]

In patients receiving moderately or highly emetogenic chemotherapy regimens, the current standard treatment for the prevention of acute CINV is combination therapy with a 5-HT_3 receptor antagonist and a corticosteroid.[1,5] For patients receiving cisplatin-based chemotherapy, this combination is generally well tolerated[1] and provides a response rate of 58–96% (based on a meta-analysis).[41] The efficacy of agents for the prevention of delayed

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CINV with highly emetogenic agents is less satisfactory.[40] The most recent published guidelines recommend the use of a corticosteroid for 3 or 4 days in conjunction with either metoclopramide for 2–4 days or a 5-HT_3 receptor antagonist for 2 or 3 days;[7] however, when these guidelines were written there were no agents approved specifically for the prevention of delayed CINV.[45] This treatment approach provides a control rate of 50 to >70%.[7]

When receiving highly emetogenic chemotherapy, a number of patients receiving antiemetic therapy still experience CINV, in particular delayed CINV. This unmet need, together with research focusing on the role of neurokinin receptors in emesis, has led to the development and investigation of NK_1 receptor antagonists.[9] In contrast to 5-HT_3 receptor antagonists, which primarily affect acute emesis in animal models, NK_1 receptor antagonists display activity against both acute and delayed emesis.[9] Because 5-HT_3 receptor antagonists do not provide complete control of CINV and have a different mechanism of action to NK_1 receptor antagonists, the efficacy of these agents administered as combination regimens has been investigated in the prevention of CINV.[46]

Aprepitant is the first commercially available NK_1 receptor antagonist. The drug antagonises the effects of substance P, a neurotransmitter which is thought to be involved in emesis. Aprepitant in combination with ondansetron and dexamethasone is effective in the prevention of acute and delayed CINV after high-dose cisplatin, and produced higher response rates than ondansetron plus dexamethasone alone (based on three well controlled trials in adults, section 4). Importantly, this preventative efficacy was maintained across multiple cycles of chemotherapy (based on small patient numbers). The addition of aprepitant to ondansetron and dexamethasone reduced the impact of CINV on patients' daily lives (section 4.2.1).

Aprepitant is generally well tolerated by patients receiving emetogenic chemotherapy (section 5). Asthenia or fatigue occurred numerically more frequently in patients receiving aprepitant plus standard therapy compared with those receiving standard therapy alone. Other adverse events associated with aprepitant include anorexia, constipation, diarrhoea, nausea (after day 5 of the study) and hiccups. In one trial, more patients receiving aprepitant plus standard therapy than those receiving standard therapy plus placebo experienced serious infection-related events; the study authors assumed this was because of pharmacokinetic interactions between aprepitant and dexamethasone. In subsequent phase III trials, in which the dexamethasone regimen was modified, there was no difference between the aprepitant groups and the standard therapy groups in the incidence of serious infections. Aprepitant's use is complicated by its propensity to interact with numerous drugs that affect or are affected by the CYP450 isoenzymes. Care will need to be taken in the administration of aprepitant with certain other drugs as it is a substrate for, and a moderate inhibitor and inducer of, CYP3A4 and an inducer of CYP2C9 (section 3.3).

Aprepitant is poorly soluble in aqueous solutions, and therefore can only be given orally.[11] Although oral antiemetic agents are generally preferred, there are times when the intravenous route may be useful.[4] A readily soluble prodrug of aprepitant is currently being evaluated in clinical trials.[11]

The most recent published guidelines recommending treatment for the prevention of CINV were published before aprepitant was approved for use. However, a recent review article[1] and an editorial[47] both stated that an NK_1 receptor antagonist should be added to standard therapy for the prevention of delayed CINV with highly emetogenic chemotherapy, particularly cisplatin-based therapy. Because aprepitant represents a new class of drugs, there are several areas in which research would be beneficial. The efficacy of aprepitant plus a corticosteroid in the prevention of delayed CINV has not yet been compared with that of the combinations recommended in treatment guidelines (a corticosteroid plus either metoclopramide or a 5-HT_3 receptor antagonist for several days).[47] Data on the use of aprepitant in the prevention of nausea and vomiting induced by moderately emetogenic chemotherapy agents and by multiple-day cisplatin regimens

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would be useful. Aprepitant has not been evaluated for longer than 5 days per cycle or for the treatment of established emesis and nausea in patients receiving emetogenic chemotherapy. As yet there are no pharmacoeconomic data available for the drug.

In conclusion, when added to standard therapy (a 5-HT_3 receptor antagonist and a corticosteroid), aprepitant is effective and generally well tolerated in the prevention of CINV associated with highly emetogenic chemotherapy in adults. Despite marked advances in the prevention of CINV, standard therapy does not protect all patients. The addition of aprepitant to standard therapy provides an advance in the prevention of both acute and delayed CINV in adults with cancer.

References

1. Stieler JM, Reichardt P, Riess H, et al. Treatment options for chemotherapy-induced nausea and vomiting: current and future. Am J Cancer 2003; 2 (1): 15-26
2. Schnell FM. Chemotherapy-induced nausea and vomiting: the importance of acute antiemetic control. Oncologist 2003; 8 (2): 187-98
3. Bender CM, McDaniel RW, Murphy-Ende K, et al. Chemotherapy-induced nausea and vomiting. Clin J Oncol Nurs 2002; 6 (2): 94-102
4. American Society of Health-System Pharmacists. ASHP therapeutic guidelines on the pharmacologic management of nausea and vomiting in adult and pediatric patients receiving chemotherapy or radiation therapy or undergoing surgery. Am J Health Syst Pharm 1999 Apr 15; 56: 729-64
5. Gralla RJ. New agents, new treatments and antiemetic therapy. Semin Oncol 2002 Feb; 29 (1 Suppl. 4): 119-24
6. European Society of Medical Oncology. Minimum clinical recommendations for prophylaxis of chemotherapy-induced nausea and vomiting (NV) [online]. Available from URL: http://www.esmo.org/reference/referenceGuidelines/html/MCR13.htm [Accessed 2003 Aug 7]
7. Gralla RJ, Osoba D, Kris MG, et al. Recommendations for the use of antiemetics: evidence-based clinical practice guidelines. American Society of Clinical Oncology. J Clin Oncol 1999 Sep; 17 (9): 2971-94
8. National Comprehensive Cancer Network. Nausea and vomiting: treatment guidelines for patients with cancer, version 1 [online]. Available from URL: http://www.cancer.org/downloads/CRI/NCCN_nausea.pdf [Accessed 2003 Aug 5]
9. Hesketh PJ. Potential role of the NK1 receptor antagonists in chemotherapy-induced nausea and vomiting. Support Care Cancer 2001 Jul; 9 (5): 350-4
10. Hesketh PJ, Van Belle S, Aapro M, et al. Differential involvement of neurotransmitters through the time course of cisplatin-induced emesis as revealed by therapy with specific receptor antagonists. Eur J Cancer 2003 May; 39 (8): 1074-80
11. Sorbera LA, Castaner J, Bayes M, et al. Aprepitant and L-758298: antiemetic, antidepressant, tachykinin NK1 antagonist. Drugs Future 2002; 27 (3): 211-22
12. Diemunsch P, Grelot L. Potential of substance P antagonists as antiemetics. Drugs 2000 Sep; 60 (3): 533-46
13. Kramer MS, Cutler N, Feighner J, et al. Distinct mechanism for antidepressant activity by blockade of central substance P receptors. Science 1998 Sep 11; 281: 1640-5
14. Rupniak NMJ, Kramer MS. Discovery of the antidepressant and anti-emetic efficacy of substance P receptor (NK1) antagonists. Trends Pharmacol Sci 1999 Dec; 20 (12): 485-90
15. Rizk AN, Hesketh PJ. Antiemetics for cancer chemotherapy-induced nausea and vomiting: a review of agents in development. Drugs RD 1999 Oct; 2 (4): 229-35
16. Kohler DR, Hughes TE. Pharmacy update: aprepitant (Emend) – review of a new antiemetic agent and guidelines for use at the NIH clinical center [online]. Available from URL: http://www.cc.nih.gov/phar/updates/mayjune03 [Accessed 2003 Sep 29]
17. Merck & Co. Inc. EMEND® (aprepitant) capsules: prescribing information. USA [online]. Available from URL: http://www.merck.com [Accessed 2003 Sep 10]
18. Tattersall FD, Rycroft W, Cumberbatch M, et al. The novel NK1 receptor antagonist MK-0869 (L-754,030) and its water soluble phosphoryl prodrug, L-758,298, inhibit acute and delayed cisplatin-induced emesis in ferrets. Neuropharmacology 2000 Feb 14; 39 (4): 652-63
19. Hale JJ, Mills SG, MacCoss M, et al. Structural optimization affording 2-(R)-(1-(R)-3, 5-bis(trifluoromethyl)-phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-oxo-1,2,4-triazol-5-yl)methylmorpholine, a potent, orally active, long-acting morpholine acetal human NK-1 receptor antagonist. J Med Chem 1998 Nov 5; 41 (23): 4607-14
20. Hale JJ, Mills SG, MacCoss M, et al. Phosphorylated morpholine acetal human neurokinin-1 receptor antagonists as water-soluble prodrugs. J Med Chem 2000 Mar 23; 43 (6): 1234-41
21. Majumdar AK, McCrea JB, Panebianco DL, et al. Effects of aprepitant on cytochrome P450 3A4 activity using midazolam as a probe. Clin Pharmacol Ther 2003 Aug; 74 (2): 150-6
22. McCrea JB, Majumdar AK, Goldberg MR, et al. Effects of the neurokinin1 receptor antagonist aprepitant on the pharmacokinetics of dexamethasone and methylprednisolone. Clin Pharmacol Ther 2003 Jul; 74 (1): 17-24
23. Blum RA, Majumdar A, McCrea J, et al. Effects of aprepitant on the pharmacokinetics of ondansetron and granisetron in healthy subjects. Clin Ther 2003 May; 25: 1407-19
24. Feuring M, Lee Y, Orlowski LH, et al. Lack of effect of aprepitant on digoxin pharmacokinetics in healthy subjects. J Clin Pharmacol 2003 Aug; 43 (8): 912-7
25. Merck Sharp and Dohme Ltd (UK). Emend: summary of product characteristics [online]. Available from URL: http://www.emea.eu.int/humandocs/Humans/EPAR/emend/emend.htm [Accessed 2003 Nov 25]
26. Chawla SP, Grunberg SM, Gralla RJ, et al. Establishing the dose of the oral NK1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting. Cancer 2003 May 1; 97 (9): 2290-300
27. de Wit R, Herrstedt J, Rapoport B, et al. Addition of the oral NK1 antagonist aprepitant to standard antiemetics provides protection against nausea and vomiting during multiple cycles of cisplatin-based chemotherapy. J Clin Oncol 2003 Nov 15; 21 (22): 4105-11
28. Poli-Bigelli S, Rodrigues-Pereira J, Carides AD, et al. Addition of the neurokinin 1 receptor antagonist aprepitant to standard antiemetic therapy improves control of chemotherapy-induced nausea and vomiting. Cancer 2003 Jun 15; 97 (12): 3090-8

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29. Navari RM, Reinhardt RR, Gralla RJ, et al. Reduction of cisplatin-induced emesis by a selective neurokinin-1-receptor antagonist: L-754,030 Antiemetic Trials Group. N Engl J Med 1999 Jan 21; 340 (3): 190-5

30. Van Belle S, Lichinitser MR, Navari RM, et al. Prevention of cisplatin-induced acute and delayed emesis by the selective neurokinin-1 antagonists, L-758,298 and MK-869. Cancer 2002 Jun 1; 94 (11): 3032-41

31. Campos D, Pereira JR, Reinhardt RR, et al. Prevention of cisplatin-induced emesis by the oral neurokinin-1 antagonist, MK-869, in combination with granisetron and dexamethasone or with dexamethasone alone. J Clin Oncol 2001 Mar 15; 19 (6): 1759-67

32. Hesketh PJ, Grunberg SM, Gralla RJ, et al. The oral neurokinin-1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting: a multinational, randomised, double-blind, placebo-controlled trial in patients receiving high-dose cisplatin – the Aprepitant Protocol 052 Study Group. J Clin Oncol 2003 Nov 15; 21 (22): 4112-9

33. Cocquyt V, Van Belle S, Reinhardt RR, et al. Comparison of L-758,298, a prodrug for the selective neurokinin-1 antagonist, L-754,030, with ondansetron for the prevention of cisplatin-induced emesis. Eur J Cancer 2001 May; 37 (7): 835-42

34. Martin AR, Carides AD, Pearson JD, et al. Functional relevance of antiemetic control: experience using the FLIE questionnaire in a randomised study of the NK-1 antagonist aprepitant. Eur J Cancer 2003 Jul; 39 (10): 1395-401

35. Grunberg SM, Hesketh PJ, Carides AD, et al. Relationships between the incidence and control of cisplatin-induced acute vomiting and delayed vomiting: analysis of pooled data from two phase III studies of the NK-1 antagonist aprepitant [abstract no. 2931]. Proc Am Soc Clin Oncol 2003; 22: 729

36. de Wit R, Herrstedt J, Rapoprt B, et al. The oral NK1 antagonist, aprepitant, given with standard antiemetics provides protection against nausea and vomiting over multiple cycles of cisplatin-based chemotherapy: a combined analysis of 2 randomised, placebo-controlled clinical trials. Eur J Cancer 2004; 40: 403-10

37. Martin AR, Ma JG, Carides AD, et al. The oral NK1 antagonist, aprepitant, was effective in maintaining patients' daily life activities in both male and female patients receiving highly emetogenic chemotherapy [abstract no. 3016]. Proc Am Soc Clin Oncol 2003 May 31; 22: 750

38. European Society of Medical Oncology (ESMO). Recommendations for prophylaxis of chemotherapy-induced nausea and vomiting (NV). Ann Oncol 2001 Aug; 12 (8): 1059-60

39. Cancer Care Ontario practice guidelines initiative: use of 5-HT3 receptor antagonists in patients receiving moderately or highly emetogenic chemotherapy [online]. Available from URL: http://www.cancercare.on.ca/pdf/full12_3.pdf [Accessed 2003 Sep 15]

40. Markman M. Progress in preventing chemotherapy-induced nausea and vomiting. Cleve Clin J Med 2002 Aug; 69 (8): 609-10, 612, 615-7

41. Jantunen IT, Kataja VV, Muhonen TT. An overview of randomised studies comparing 5-HT3 receptor antagonists to conventional anti-emetics in the prophylaxis of acute chemotherapy-induced vomiting. Eur J Cancer 1997 Jan; 33 (1): 66-74

42. Oettle H, Riess H. Treatment of chemotherapy-induced nausea and vomiting. J Cancer Res Clin Oncol 2001; 127 (6): 340-5

43. MGI Pharma Inc. Aloxi palonosetron HCl injection: prescribing information (USA) [online]. Available from URL: http://www.aloxi.com/downloads/Aloxi_Prescribing_Information.pdf [Accessed 2003 Sep 1]

44. Marek C. Antiemetic therapy in patients receiving cancer chemotherapy. Oncol Nurs Forum 2003; 30 (2): 259-71

45. Merck. Emend drug interaction studies advised by Cmte, approval supported. FDC Pink 2003 Mar 10; 65: 14

46. Stahl SM. The ups and downs of novel antiemetic drugs. Part 1: substance P, 5-HT, and the neuropharmacology of vomiting. J Clin Psychiatry 2003 May; 64 (5): 498-9

47. Kris M. Why do we need another antiemetic? Just ask. J Clin Oncol 2003 Nov 15; 21 (22): 4077-80

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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Thomas B. Ottoboni et al.	Examiner: Miriam A. Levin	
Application No.:	15/083,071	Art Unit: 1613	
Filed:	March 28, 2016	CONF. NO: 9469	
FOR:	**EMULSION FORMULATIONS OF APREPITANT**		

DECLARATION UNDER 37 C.F.R. §1.132

Mail Stop: Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Madam:

I, Thomas Ottoboni, declare as follows:

1. I currently hold the position of Senior Vice President at Heron Therapeutics and have been employed by Heron Therapeutics (formerly A. P. Pharma) since 2012. In my position at Heron Therapeutics, I supervise a group of 10 scientists responsible for the development of new products. This encompasses formulation development, analytical chemistry, as well as all preclinical evaluations.

2. My academic credentials include a Ph.D. in organic chemistry (U.C. Berkeley), a master of science (M.S.) degree in organic chemistry (S.F. State University), and a bachelor of science (B.S.) degree (U. C. Berkeley).

3. I am an inventor or co-inventor on 21 issued U.S. patents and on 14 pending U.S. patent publications directed to a variety of technologies including contrast agents, microparticles, emulsions, drug delivery, pharmaceuticals, and polyorthoester-based delivery systems.

4. I am a co-author of seven technical publications in various peer-reviewed journals including *J Exp Pharmacology, Contrast Media Mol Imaging, Magn Reson Med.*, and *Tetrahedron Letters,* and have presented scientific talks at numerous scientific meetings

including the Annual Scientific Sessions of the American Heart Association, the Annual Scientific Sessions of the American Society of Echocardiography, and the Scientific Meeting of the International Society for Magnetic Resonance in Medicine.

5. My Curriculum Vitae is attached hereto as Exhibit A.

6. I am a named co-inventor in the instant patent application, U.S. Application No. 15/083,071. I am familiar with the contents of the pending application, and have read and understand the claims that are currently pending in the instant application. I have also reviewed and am familiar with both the Examiner's remarks in the non final Office action mailed June 3, 2016 (hereinafter "non final Office action") and the art cited therein. I was also present during the telephonic interview held with Examiner Levin held on August 25, 2016 and have read the Examiner's Interview Summary mailed August 31, 2016 (hereinafter "Examiner Interview Summary").

7. The Examiner has identified Zhou (Chinese patent application publication number CN 102379845, an English translation of which was submitted by Applicants in the IDS dated April 12, 2016) as the primary reference in a rejection under 35 U.S.C. § 103(a) in the non final Office action. Zhou describes oil-in-water emulsions of aprepitant and provides 8 examples describing preparation of aprepitant emulsions. Zhou teaches an aprepitant emulsion which comprises 0.5 to 2.0 wt%, preferably 1.0 to 1.5 wt% aprepitant, 5 to 30 wt%, preferably 7 to 15 wt% oil, wherein the oil is soybean oil, 0.5 to 10 wt%, preferably 8 to 10 wt% emulsifier, wherein the emulsifier is egg yolk phospholipids, 1 to 10 wt%, preferably 2 to 5 wt% co-emulsifier, wherein the co-emulsifier is ethanol, and 5 to 20 wt%, preferably 8 to 13 wt% protective agent, wherein the protective agent may be glycerin, sucrose or glucose. The pH of the emulsion is 6.0 to 8.0.

8. The Examiner stated in the non final Office action that the only ingredient recited in the instant claims with a range that does not at least touch the range taught by Zhou is that of the emulsifier. The Examiner further states that Zhou teaches 0.5 to 10 wt% emulsifier, preferably 8 to 10 wt% wherein the emulsifier is egg yolk phospholipids. The instant claims recite 13 to 15 wt% egg yolk lecithin.

9. During the telephonic interview, I explained that the instant claims were not obvious over Zhou for at least the reason that the claimed pharmaceutical emulsion possessed unexpected and unpredictable properties relative to Zhou. Specifically, as summarized in Table 7 of the

instant specification as filed, the pharmaceutical aprepitant emulsions prepared as described in Examples 1, 2, 3, and 6 were stable at room temperature for at least 2 months. In contrast, the aprepitant emulsions taught by Zhou were not stable. We discovered this problem with the emulsions of Zhou by preparing emulsions as taught by Zhou. Two emulsion formulations which comprise the ingredients taught by Zhou were prepared and are described in Examples 4 and 5 of the instant application. The Examples show that emulsions according to the teachings of Zhou are not stable and form crystals within 4 days of storage at room temperature.

10. The Examiner asked about possible differences between the preparation method described by Zhou, specifically Example 1 in Zhou, and the preparation method described in Example 4 of the instant application. The Examiner requested that I submit a declaration to provide clarity regarding the teachings of Zhou and to show that the methods of Zhou were the same as those used in Example 4 of the instant application in order to support the argument that the claimed range of 13 to 15 wt% egg yolk lecithin results in an unpredictable increase in stability of the claimed pharmaceutical aprepitant emulsion in view of Zhou.

11. The Examiner noted that Zhou teaches that "soybean oil was added to the coarse emulsion and an appropriate amount of ethanol was added to dissolve the [sic] them." The Examiner noted during the telephonic interview that Example 4 of the instant specification does not teach adding soybean oil to the emulsion but then also noted in the Examiner Interview Summary dated August 31, 2016 that the preparation of Example 2 "does not have two phases at that point." I have carefully read Example 2 of Zhou and my understanding is that the phrase "soybean oil was added to the coarse emulsion" represents an inaccuracy in translation with respect to the use of the word "emulsion" because up to this point it is clear that no emulsion (mixture of an oil phase and an aqueous phase) exists. Instead, soybean oil is being added to a mixture of aprepitant, egg yolk phospholipid (the ethanol added with the aprepitant and egg yolk phospholipid had evaporated) to generate the oil phase. Accordingly, Example 4 of the instant application followed a procedure identical to Example 2 of Zhou in that aprepitant, egg yolk lecithin and ethanol were combined, dissolved by heating and stirring at 60°C until the ethanol was evaporated, and the soybean oil was then added to the mixture (described as a "thick residue" in Example 4 of the instant application and described as a "coarse emulsion" in the English translation of Zhou).

12. Another potential discrepancy questioned by the Examiner between Example 4 of the instant application and Example 1 of Zhou is that Zhou appears to dissolve the "sticky residue with soybean oil and ethanol before heating," but Example 4 of the instant application appears to require heating to dissolve the material. When I read Zhou Example 1, my understanding of the phrase "soybean oil was added to the coarse emulsion and an appropriate amount of ethanol was added to dissolve the them" describes the function of the soybean oil and ethanol, and that heating at 60°C was necessary to fully dissolve the oil and ethanol in the prepared mixture of aprepitant and egg yolk lecithin. Zhou did not intend to suggest or describe dissolution of the soybean oil and ethanol in the mixture of aprepitant and egg yolk lecithin prior to heating. Again, I believe that the aprepitant emulsion described in Example 4 was prepared in the same manner as the aprepitant emulsion prepared in Zhou.

13. Accordingly, based upon my knowledge and expertise in the area of organic chemistry and the preparation of pharmaceutical emulsions, it is my opinion that the methods taught by Zhou in at least Example 1 do not differ from the method taught in Example 4 of the instant specification.

14. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true. I declare that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the instant application or any patent issuing thereon.

Aug 31 2016
Date

Thomas Ottoboni, Ph.D.

APPENDIX A

Thomas Ottoboni Ph.D.

Professional Profile

- Ph.D. in organic chemistry with a broad scientific background and a registered patent agent.
- Conceived and developed multiple product technology platforms in the pharmaceutical and medical device fields.
- Extensive experience in pharmaceutical and medical device development with hands-on roles in all aspects of R&D, manufacturing, quality, regulatory affairs, and intellectual property management.

Education

- Ph.D. Chemistry. University of California, Berkeley, 1986. Organic Chemistry
- M.S. Chemistry. San Francisco State University, 1982. Organic Chemistry
- B.S. Chemistry. University of California Berkeley, 1981.

Professional Certification

- Registered to Practice before the USPTO, Reg. No. 64987

US Patents and Applications

8,486,444	Nanobubbles useful as an ultrasonic contrast agent for the lymphatic system
8,460,637	Reconstitutable microsphere compositions useful as ultrasonic contrast agents
6,896,659	Method for ultrasound triggered drug delivery using hollow microspheres.
6,776,761	Hollow microspheres with controlled fragility for medical use
6,524,608	Intravesical drug delivery system
6,482,518	Excipient for the lyophilization of aqueous suspensions of microparticles
6,207,180	Intravesical drug delivery
6,193,951	Microparticles useful as ultrasonic contrast agents
6,039,967	Intravesical drug delivery system
5,977,171	Sustained release emulsions
5,977,044	Liquid peracid precursor colloidal dispersions: macroemulsions
5,837,226	Ocular microsphere delivery system
5,776,877	Liquid peracid precursor colloidal dispersions: macroemulsions
5,767,153	Sustained release emulsions
5,731,005	Hydrogel-based microsphere drug delivery systems
5,710,296	Process for preparing phenyl esters
5,667,735	Opthalmic mold coatings
5,551,663	Plastic molds for ophthalmic devices and methods for forming same
5,459,176	Radiation curable coating for plastic articles
5,415,796	Liquid nonaqueous detergent with stable, solubilized peracid
5,269,962	Oxidant composition containing stable bleach activator granules

20070243138	Hollow microspheres with controlled fragility for medical use
20060241466	Hollow microspheres with controlled fragility for medical use
20050113697	Method of imaging lymphatic system using nanocapsule compositions
20050106105	Methods and compositions for ultrasound imaging of apoptosis
20040185108	Method of preparing gas-filled polymer matrix microparticles useful for delivering drug
20040086459	Microparticles useful as ultrasonic contrast agents
20030215394	Microparticles having a matrix interior useful for ultrasound triggered delivery of drugs into the bloodstream
20030036697	Hollow microspheres with controlled fragility for medical use
20020151792	Method for ultrasound triggered drug delivery using hollow microbubbles with controlled fragility
20010012522	Microparticles useful as ultrasonic contrast agents and for delivery of drugs into the bloodstream
20140161726	Reconstitutable Microsphere Compositions Useful As Ultrasonic Contrast Agents
20140275145	Compositions of a polyorthoester and an aprotic solvent
20140275046	Compositions of a polyorthoester and an aprotic solvent
20140296282	Compositions of a polyorthoester and an aprotic solvent
20150297729	Long-acting polymeric delivery systems
20150297730	Compositions of a polyorthoester and an organic acid excipient
20150320866	Pharmaceutical composition comprising antiemetic compounds and polyorthoester
20160082013	Emulsion formulations of aprepitant
20160206622	Emulsion formulations of aprepitant
20160206761	Reconstitutable Microsphere Compositions Useful As Ultrasonic Contrast Agents

Publications and Presentations

Peer Reviewed Publications

Biochronomer™ technology and the development of APF530, a sustained release formulation of granisetron. Ottoboni T, Gelder M, O'Boyle E., *J Exp Pharmacology.* **2014**, 2014(6), 15-21

Characterization of the in vitro adherence behavior of ultrasound responsive double-shelled microspheres targeted to cellular adhesion molecules. Ottoboni S, Short RE, Kerby MB, Tickner EG, Steadman E, Ottoboni TB., *Contrast Media Mol Imaging.* **2006**, 1(6):279-90.

Sentinel node detection using contrast-enhanced power Doppler ultrasound lymphography. Wisner ER, Ferrara KW, Short RE, Ottoboni TB, Gabe JD, Patel D. *Invest Radiol.* **2003**, 38(6):358-65.

Contrast enhanced intermittent power Doppler ultrasound with sub-micron bubbles for sentinel node detection. Wisner ER, Ferrara K, Gabe JD, Patel D, Nyland TG, Short RE, Ottoboni TB. *Acad Radiol.* **2002**, 9 Suppl 2:S389-91.

Hyperpolarized ^{3}He microspheres as a novel vascular signal source for MRI. Chawla MS, Chen XJ, Cofer GP, Hedlund LW, Kerby MB, Ottoboni TB, Johnson GA. *Magn Reson Med.* **2000**, 43(3):440-5.

Betaine:homocysteine methyltransferase from rat liver: purification and inhibition by a boronic acid substrate analog. Lee KH, Cava M, Amiri P, Ottoboni T, Lindquist RN. *Arch Biochem Biophys.* **1992**, 292(1):77-86.

Organic Reactions Under High Pressure. A Mild Method for the Placement of Protecting Groups on Hindered and Sensitive Alcohols. Dauben, W.G.; Bunce, R.A.: Gerdes, J.M.; Henegar, K.E.: Cunningham. A.F.; Ottoboni, T.B. *Tetrahedron Letters* **1982**, *24*, 5709.

Presentations

Detection of Recent Myocardial Ischemia Using a New Contrast Agent Designed for Human Application. Xiaoping Leng; Jianjun Wang; Carson Andrew; Michelle Grata; Abigail Schwartz; Huili Fu; Linda Lavery; Xucai Chen; Sue Ottoboni; Tom Ottoboni; William R Wagner; Flordeliza S Villanueva. American Heart Association, Annual Scientific Sessions 2010

Fate of Targeted Ultrasound Contrast Agents after Endothelial Adhesion: A Time Course Study. Shivani Bowry; Jianjun Wang; Sue Ottoboni; Tom Ottoboni; William R Wagner; Flordeliza Villanueva. American Heart Association, Annual Scientific Sessions 2007

Targeted Ultrasound Imaging of Apoptosis in Acute Myocardial Injury with Annexin-A5-Microspheres. Verjans JW, Haider N, Li P, Narula N, Brittin R, Gabe J, Ottoboni TB, Hofstra L, Reutelingsperger C, Narula J, Vannan MA. American Heart Association, Annual Scientific Sessions, 2004

Noninvasive in vivo ultrasound imaging of apoptosis in acute myocardial infarction with annexin-V conjugated microbubbles. Verjans W, Haider N, Peng L, Narula N, Robin, Gabe J, Ottoboni T, Hoffstra L, Reutelingsperger C, Maastricht, Narula J, Vannan MA. Annual Scientific Sessions, American Society of Echocardiography, 2004

Evaluation of Cardiac Function and Morphology During Myocardial Contrast Echocardiography with Cardiosphere® in Anesthetized Dogs. Goldman, JH; del Balzo; U; Ottoboni, TB. Annual Meeting of the European Society of Cardiology, 2006

Hemodynamic and Toxicology studies of PB127, a double shell ultrasound contrast agent containing nitrogen, Jonathan Goldman, Mary Treuhaft, Edward Koo, Brian Rogers, Roger Culbertson, Jerry Griffin, Thomas Ottoboni. American Heart Association, Annual Scientific Sessions 2002

Perfusion Assessment using Hyperpolarized 3He Microspheres. M.S. Chawla, G.P. Cofer, L.W. Hedlund, J.K. Tajik, M.B. Kerby, T.B. Ottoboni, G.A. Johnson. Scientific Meeting of the International Society for Magnetic Resonance in Medicine 2000

Professional Experience

Heron Therapeutics

Senior Vice President, Preclinical and Pharmaceutical Development	2014-Present
Vice President, Pharmaceutical Development	2012-2014
Independent Consultant to the Pharmaceutical Industry	2008-2010

Point Biomedical Corporation, San Carlos CA

Executive Vice President, Operations	2002-2008
Vice President, Research and Development	1996-2000

bioMosaic Systems, Belmont CA

Founder, President	2000-2001

InSite Vision, Alameda CA

Manager, Systems Development	1994-1996

Soane Technologies, Hayward CA

Project Leader, Materials Development	1993-1994
Vitaphore Corp., Menlo Park CA	
Director, Drug Delivery	1991-1993
Senior Chemist	
The Clorox Company, Pleasanton CA	
Senior Scientist	1986-1991

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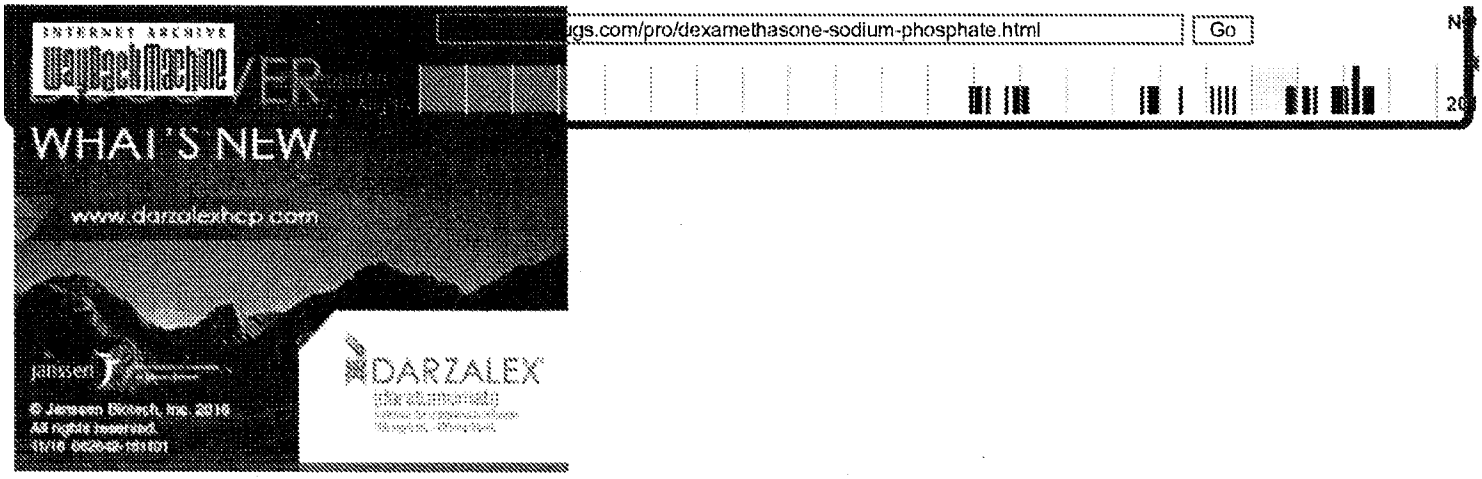
Dexamethasone Sodium Phosphate

Pronunciation

Dosage Form: injection, solution

- Overview
- Side Effects
- Dosage
- Interactions
- For Professionals
- More
  - Pregnancy Warnings
  - Breastfeeding Warnings
  - User Reviews
  - Drug Images
  - Support Group Q & A
  - Pricing & Coupons

Dexamethasone Sodium Phosphate Injection USP



Dexamethasone Sodium Phosphate Description

Dexamethasone Sodium Phosphate is a water-soluble inorganic ester of dexamethasone. It occurs as a white or slightly yellow crystalline powder, is odorless or has a slight odor of alcohol, is exceedingly hygroscopic and is freely soluble in water.

Dexamethasone Sodium Phosphate is an adrenocortical steroid anti-inflammatory drug.

Chemically, Dexamethasone Sodium Phosphate is 9-Fluoro-11ß,17,21-trihydroxy-16α-methylpregna-1, 4-diene-3,20-dione 21-(dihydrogen phosphate) disodium salt and has the following structural formula:

Slideshow: Worried About Ebola? You're More Likely to Get These 10 Serious Infections

Worried About Ebola? You're More Likely to Get These 10 Serious Infections

Dexamethasone Sodium Phosphate Injection, USP is a sterile solution of Dexamethasone Sodium Phosphate in water for injection for intravenous (IV), intramuscular (IM), intra-articular, soft-tissue or intralesional use.

Each mL contains Dexamethasone Sodium Phosphate equivalent to dexamethasone phosphate 4 mg or dexamethasone 3.33 mg; benzyl alcohol 10 mg added as preservative; sodium citrate dihydrate 11 mg; sodium sulfite 1 mg as an antioxidant; Water for Injection q.s. Citric acid and/or sodium hydroxide may have been added for pH adjustment (7.0 to 8.5). Air in th container is displaced by nitrogen.

Dexamethasone Sodium Phosphate - Clinical Pharmacology

INTERNET ARCHIVE http://www.drugs.com/pro/dexamethasone-sodium-phosphate.html 35 captures 23 Dec 07 - 7 Aug 16

Dexamethasone Sodium Phosphate has a rapid onset but short duration of action when compared with less soluble preparations. Because of this, it is suitable for the treatment of acute disorders responsive to adrenocortical steroid therapy.

Naturally occurring glucocorticoids (hydrocortisone and cortisone) possess both glucocorticoid and mineralocorticoid properties and are used in replacement therapy in adrenocortical deficiency states. Their synthetic analogs, including dexamethasone, are primarily used for their potent anti-inflammatory effects in disorders of many organ systems.

Glucocorticoids cause profound and varied metabolic effects. In addition, they modify the body's immune responses to diverse stimuli.

At equipotent anti-inflammatory doses, dexamethasone almost completely lacks the sodium-retaining property of hydrocortisone and closely related derivatives of hydrocortisone.

Indications and Usage for Dexamethasone Sodium Phosphate

Intravenous or Intramuscular Injection

When oral therapy is not feasible and the strength, dosage form, and route of administration of the drug reasonably lend the preparation to the treatment of the condition, those products labeled for intravenous or intramuscular use are indicated as follows:

• Endocrine Disorders

Primary or secondary adrenocortical insufficiency (hydrocortisone or cortisone is the drug of choice; synthetic analogs may be used in conjunction with mineralocorticoids where applicable; in infancy, mineralocorticoid supplementation is of particular importance)

Acute adrenocortical insufficiency (hydrocortisone or cortisone is the drug of choice; mineralocorticoid supplementation may be necessary, particularly when synthetic analogs are used)

Preoperatively, and in the event of serious trauma or illness, in patients with known adrenal insufficiency or when adrenocortical reserve is doubtful

Shock unresponsive to conventional therapy if adrenocortical insufficiency exists or is suspected

Congenital adrenal hyperplasia

Nonsuppurative thyroiditis

Hypercalcemia associated with cancer

• Rheumatic Disorders

As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in:

Post-traumatic osteoarthritis

Synovitis of osteoarthritis

Rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy)

Acute and subacute bursitis

Epicondylitis

Acute nonspecific tenosynovitis http://www.drugs.com/pro/dexamethasone-sodium-phosphate.html Go
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Psoriatic arthritis

Ankylosing spondylitis

• Collagen Diseases

During an exacerbation or as maintenance therapy in selected cases of:

Systemic lupus erythematosus

Acute rheumatic carditis

• Dermatologic Diseases

Pemphigus

Severe erythema multiforme (Stevens-Johnson syndrome)

Exfoliative dermatitis

Bullous dermatitis herpetiformis

Severe seborrheic dermatitis

Severe psoriasis

Mycosis fungoides

• Allergic States

Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment in:

Bronchial asthma

Contact dermatitis

Atopic dermatitis

Serum sickness

Seasonal or perennial allergic rhinitis

Drug hypersensitivity reactions

Urticarial transfusion reactions

Acute noninfectious laryngeal edema (epinephrine is the drug of first choice)

• Ophthalmic Diseases

Severe acute and chronic allergic and inflammatory processes involving the eye, such as:

Herpes zoster ophthalmicus

Iritis, iridocyclitis

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Optic neuritis

Sympathetic ophthalmia

Anterior segment inflammation

Allergic conjunctivitis

Keratitis

Allergic corneal marginal ulcers

• Gastrointestinal Diseases

To tide the patient over a critical period of the disease in:

Ulcerative colitis (Systemic therapy)

Regional enteritis (Systemic therapy)

• Respiratory Diseases

Symptomatic sarcoidosis

Berylliosis

Fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy Loeffler's syndrome not manageable by other means

Aspiration pneumonitis

• Hematologic Disorders

Acquired (autoimmune) hemolytic anemia Idiopathic thrombocytopenic purpura in adults (IV only; IM administration is contraindicated)

Secondary thrombocytopenia in adults

Erythroblastopenia (RBC anemia)

Congenital (erythroid) hypoplastic anemia

• Neoplastic Diseases

For palliative management of:

Leukemias and lymphomas in adults

Acute leukemia of childhood

• Edematous States

To induce diuresis or remission of proteinuria in the nephrotic syndrome, without uremia, of the idiopathic type, or that due to lupus erythematosus

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meningitis with subarachnoid block or impending block when used concurrently with

Trichinosis with neurologic or myocardial involvement

- Diagnostic testing of adrenocortical hyperfunction
- Cerebral Edema associated with primary or metastatic brain tumor, craniotomy, or head injury.

Use in cerebral edema is not a substitute for careful neurosurgical evaluation and definitive management such as neurosurgery or other specific therapy.

By Intra-articular or Soft Tissue Injection

As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in:

Synovitis of osteoarthritis

Rheumatoid arthritis

Acute and subacute bursitis

Acute gouty arthritis

Epicondylitis

Acute nonspecific tenosynovitis

Post-traumatic osteoarthritis

By Intralesional Injection

Keloids

Localized hypertrophic, infiltrated, inflammatory lesions of: lichen planus, psoriatic plaques, granuloma annulare and lichen simplex chronicus (neurodermatitis)

Discoid lupus erythematosus

Necrobiosis lipoidica diabeticorum

Alopecia areata

May also be useful in cystic tumors of an aponeurosis or tendon (ganglia)

Contraindications

Systemic fungal infections (see WARNINGS regarding amphotericin B). Hypersensitivity to any component of this product, including sulfites (see WARNINGS).

Warnings

Because rare instances of anaphylactoid reactions have occurred in patients receiving parenteral corticosteroid therapy, appropriate precautionary measures should be taken prior to administration, especially when the patient has a history of

http://www.rxlist.com/dexamethasone-sodium-phosphate-drug.htm
INTENDED USE/INDICATIONS
ADVERSE REACTIONS
35 sections
28 Dec 07 - 7 Aug 16

allergy to any drug. Anaphylactoid reactions have been reported with Dexamethasone Sodium P (See ADVERSE REACTIONS).

Dexamethasone Sodium Phosphate Injection, USP is contraindicated in systemic fungal infections and in patients who are hypersensitive to any component of this product.

Sulfite sensitivity is a known or suspected cause of life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in non-asthmatic people.

Corticosteroids may exacerbate systemic fungal infections and therefore, should not be used in the presence of such infections unless they are needed to control drug reactions due to amphotericin B. Moreover, there have been cases reported in which concomitant use of amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive failure.

In patients on corticosteroid therapy subjected to any unusual stress, increased dosage of rapidly acting corticosteroids before, during, and after the stressful situation is indicated.

Drug-induced secondary adrenocortical insufficiency may result from too rapid withdrawal of corticosteroids and may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. If the patient is receiving steroids already, dosage may have to be increased. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

Corticosteroids may mask some signs of infection, and new infections may appear during their use. There may be decreased resistance and inability to localize infection when corticosteroids are used. Moreover, corticosteroids may affect the nitroblue-tetrazolium test for bacterial infection and produce false negative results.

In cerebral malaria, a double-blind trial has shown that the use of corticosteroids is associated with prolongation of coma and a higher incidence of pneumonia and gastrointestinal bleeding.

Corticosteroids may activate latent amebiasis. Therefore, it is recommended that latent or active amebiasis be ruled out before initiating corticosteroid therapy in any patient who has spent time in the tropics or any patient with unexplained diarrhea.

Prolonged use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to fungi or viruses.

Average and large doses of cortisone or hydrocortisone can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.

Administration of live virus vaccines, including smallpox, is contraindicated in individuals receiving immunosuppressive doses of corticosteroids. If inactivated viral or bacterial vaccines are administered to individuals receiving immunosuppressive doses of corticosteroids, the expected serum antibody response may not be obtained. However, immunization procedures may be undertaken in patients who are receiving corticosteroids as replacement therapy, e.g., for Addison's disease.

Persons who are on drugs which suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in non-immune children or adults on corticosteroids. In such children or adults who have not had these diseases, particular care should be taken to avoid exposure. How the dose, route and duration of corticosteroid administration affects the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information). If chickenpox develops, treatment with antiviral agent may be considered.

http://www.drugs.com/pro/dexamethasone-sodium-phosphate.html
35 captures

The use of Dexamethasone Sodium Phosphate is also indicated for those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with an appropriate antituberculous regimen.

If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.

Literature reports suggest an apparent association between use of corticosteroids and left ventricular free wall rupture after a recent myocardial infarction; therefore, therapy with corticosteroids should be used with great caution in these patients.

Serious Neurologic Adverse Reactions with Epidural Administration

Serious neurologic events, some resulting in death, have been reported with epidural injection of corticosteroids. Specific events reported include, but are not limited to, spinal cord infarction, paraplegia, quadriplegia, cortical blindness, and stroke These serious neurologic events have been reported with and without use of fluoroscopy. The safety and effectiveness of epidural administration of corticosteroids has not been established, and corticosteroids are not approved for this use.

Pregnancy

Teratogenic Effects: Pregnancy Category C–

Since adequate human reproduction studies have not been done with corticosteroids, use of these drugs in pregnancy or in women of childbearing potential requires that the anticipated benefits be weighed against the possible hazards to the mother and embryo or fetus. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

Corticosteroids appear in breast milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other unwanted effects. Mothers taking pharmacologic doses of corticosteroids should be advised not to nurse.

Precautions

This product, like many other steroid formulations, is sensitive to heat. Therefore, it should not be autoclaved when it is desirable to sterilize the exterior of the vial.

Following prolonged therapy, withdrawal of corticosteroids may result in symptoms of the corticosteroid withdrawal syndrome including fever, myalgia, arthralgia, and malaise. This may occur in patients even without evidence of adrenal insufficiency.

There is an enhanced effect of corticosteroids in patients with hypothyroidism and in those with cirrhosis.

Corticosteroids should be used cautiously in patients with ocular herpes simplex for fear of corneal perforation.

The lowest possible dose of corticosteroid should be used to control the condition under treatment, and when reduction in dosage is possible, the reduction must be gradual.

Psychic derangements may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

Aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia.

Steroids should be used with caution in nonspecific ulcerative colitis, if there is a probability of impending perforation, abscess, or other pyogenic infection, also in diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer, renal insufficiency, hypertension, osteoporosis, and myasthenia gravis. Signs of peritoneal irritation following gastrointestinal

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perforation in patients receiving large doses of corticosteroids may be minimal or absent. Fat embolism has been reported as a complication of hypercortisonism.

When large doses are given, antacids should be administered frequently and completely between meals, and the patient should be watched for gastric irritation or bleeding. Peptic ulcer.

Growth and development of infants and children on prolonged corticosteroid therapy should be carefully followed.

Steroids may increase or decrease motility and number of spermatozoa in some patients.

Phenytoin, phenobarbital, ephedrine, and rifampin may enhance the metabolic clearance of corticosteroids resulting in decreased blood levels and lessened physiologic activity, thus requiring adjustment in corticosteroid dosage. These interactions may interfere with dexamethasone suppression tests which should be interpreted with caution during administration of these drugs.

False negative results in the dexamethasone suppression test (DST) in patients being treated with indomethacin have been reported. Thus, results of the DST should be interpreted with caution in these patients.

The prothrombin time should be checked frequently in patients who are receiving corticosteroids and coumarin anticoagulants at the same time because of reports that corticosteroids have altered the response to these anticoagulants. Studies have shown that the usual effect produced by adding corticosteroids is inhibition of response to coumarins, although there have been some conflicting reports of potentiation not substantiated by studies.

When corticosteroids are administered concomitantly with potassium-depleting diuretics, patients should be observed closely for development of hypokalemia.

Intra-articular injection of a corticosteroid may produce systemic as well as local effects.

Appropriate examination of any joint fluid present is necessary to exclude a septic process.

A marked increase in pain accompanied by local swelling, further restriction of joint motion, fever, and malaise is suggestive of septic arthritis. If this complication occurs and the diagnosis of sepsis is confirmed, appropriate antimicrobial therapy should be instituted.

Injection of a steroid into an infected site is to be avoided.

Corticosteroids should not be injected into unstable joints.

Patients should be impressed strongly with the importance of not overusing joints in which symptomatic benefit has been obtained as long as the inflammatory process remains active.

Frequent intra-articular injection may result in damage to joint tissues.

The slower rate of absorption by intramuscular administration should be recognized.

Information for Patients

Persons who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles. Patients should also be advised that if they are exposed, medical advice should be sought without delay.

Adverse Reactions

Fluid and electrolyte disturbances:

Sodium retention

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rt failure in susceptible patients

Potassium loss

Hypokalemic alkalosis

Hypertension

Musculoskeletal:

Muscle weakness

Steroid myopathy

Loss of muscle mass

Osteoporosis

Pathologic fracture of long bones

Vertebral compression fractures

Aseptic necrosis of femoral and humeral heads

Tendon rupture

Gastrointestinal:

Peptic ulcer with possible subsequent perforation and hemorrhage

Perforation of the small and large bowel, particularly in patients with inflammatory bowel disease

Pancreatitis

Abdominal distention

Ulcerative esophagitis

Dermatologic:

Impaired wound healing

Thin fragile skin

Petechiae and ecchymoses

Erythema

Increased sweating

May suppress reactions to skin tests

Burning or tingling, especially in the perineal area (after IV injection)

Other cutaneous reactions, such as allergic dermatitis, urticaria, angioneurotic edema

Neurologic:

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cranial pressure with papilledema (pseudotumor cerebri) usually after treatment

Vertigo

Headache

Psychic disturbances

Endocrine:

Menstrual irregularities

Development of cushingoid state

Suppression of growth in children

Secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery, or illness

Decreased carbohydrate tolerance

Manifestations of latent diabetes mellitus

Increased requirements for insulin or oral hypoglycemic agents in diabetics

Hirsutism

Ophthalmic:

Posterior subcapsular cataracts

Increased intraocular pressure

Glaucoma

Exophthalmos

Metabolic:

Negative nitrogen balance due to protein catabolism

Cardiovascular:

Myocardial rupture following recent myocardial infarction (see WARNINGS)

Other:

Anaphylactoid or hypersensitivity reactions

Thromboembolism

Weight gain

Increased appetite

Nausea

Malaise

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Additional adverse reactions are related to parenteral corticosteroid therapy:

Rare instances of blindness associated with intralesional therapy around the face and head

Hyperpigmentation or hypopigmentation

Subcutaneous and cutaneous atrophy

Sterile abscess

Post-injection flare (following intra-articular use)

Charcot-like arthropathy

Overdosage

Reports of acute toxicity and/or death following overdosage of glucocorticoids are rare. In the event of overdosage, no specific antidote is available; treatment is supportive and symptomatic.

The oral LD_{50} of dexamethasone in female mice was 6.5 g/kg. The intravenous LD_{50} of Dexamethasone Sodium Phosphate in female mice was 794 mg/kg.

Dexamethasone Sodium Phosphate Dosage and Administration

Dexamethasone Sodium Phosphate injection, 4 mg/mL – *For intravenous, intramuscular, intra-articular, intralesional, and soft tissue injection.*

Dexamethasone Sodium Phosphate injection can be given directly from the vial, or it can be added to Sodium Chloride Injection or Dextrose Injection and administered by intravenous drip.

Solutions used for intravenous administration or further dilution of this product should be preservative free when used in the neonate, especially the premature infant.

When it is mixed with an infusion solution, sterile precautions should be observed. Since infusion solutions generally do no contain preservatives, mixtures should be used within 24 hours.

DOSAGE REQUIREMENTS ARE VARIABLE AND MUST BE INDIVIDUALIZED ON THE BASIS OF THE DISEASE AND THE RESPONSE OF THE PATIENT.

Intravenous and Intramuscular Injection

The initial dosage of Dexamethasone Sodium Phosphate injection varies from 0.5 to 9 mg a day depending on the disease being treated. In less severe diseases doses lower than 0.5 mg may suffice, while in severe diseases doses higher than 9 mg may be required.

The initial dosage should be maintained or adjusted until the patient's response is satisfactory. If a satisfactory clinical response does not occur after a reasonable period of time, discontinue Dexamethasone Sodium Phosphate injection and transfer the patient to other therapy.

After a favorable initial response, the proper maintenance dosage should be determined by decreasing the initial dosage in small amounts to the lowest dosage that maintains an adequate clinical response.

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Patients should be observed closely for signs that require dosage adjustment, including changes in clinical status re[illegible]issions or exacerbations of the disease, individual drug responsiveness, and the effect of stress (e.g., trauma). During stress it may be necessary to increase dosage temporarily.

If the drug is to be stopped after more than a few days of treatment, it usually should be withdrawn gradually.

When the intravenous route of administration is used, dosage usually should be the same as the oral dosage. In certain overwhelming, acute, life-threatening situations, however, administration in dosages exceeding the usual dosages may be justified and may be in multiples of the oral dosages. The slower rate of absorption by intramuscular administration should be recognized.

Shock

There is a tendency in current medical practice to use high (pharmacologic) doses of corticosteroids for the treatment of unresponsive shock. The following dosages of Dexamethasone Sodium Phosphate injection have been suggested by various authors:

Author	*Dosage*
Cavanagh[1]	3 mg/kg of body weight per 24 hours by constant intravenous infusion after an initial intravenous injection of 20 mg
Dietzman[2]	2 to 6 mg/kg of body weight as a single intravenous injection
Frank[3]	40 mg initially followed by repeat intravenous injection every 4 to 6 hours while shock persists
Oaks[4]	40 mg initially followed by repeat intravenous injection every 2 to 6 hours while shock persists
Schumer[5]	1 mg/kg of body weight as a single intravenous injection

Administration of high dose corticosteroid therapy should be continued only until the patient's condition has stabilized and usually not longer than 48 to 72 hours.

Although adverse reactions associated with high dose, short term corticosteroid therapy are uncommon, peptic ulceration may occur.

Cerebral Edema

Dexamethasone Sodium Phosphate injection is generally administered initially in a dosage of 10 mg intravenously followed by four mg every six hours intramuscularly until the symptoms of cerebral edema subside. Response is usually noted within 12 to 24 hours and dosage may be reduced after two to four days and gradually discontinued over a period of five to seven days. For palliative management of patients with recurrent or inoperable brain tumors, maintenance therapy with two mg two or three times a day may be effective.

Allergic Disorders http://www.drugs.com/pro/dexamethasone-sodium-phosphate.html Go
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In acute, self-limited allergic disorders or acute exacerbations of chronic allergic disorders, the following dosage schedules combining parenteral and oral therapy is suggested:

Dexamethasone Sodium Phosphate injection, 4 mg/mL: *first day*, 1 or 2 mL (4 or 8 mg), intramuscularly.

Dexamethasone tablets, 0.75 mg: second and third days, 4 tablets in two divided doses each day; fourth day, 2 tablets in two divided doses; fifth and sixth days, 1 tablet each day; seventh day, no treatment; eighth day, follow-up visit.

This schedule is designed to ensure adequate therapy during acute episodes, while minimizing the risk of overdosage in chronic cases.

Intra-articular, Intralesional and Soft Tissue Injection

Intra-articular, intralesional, and soft tissue injections are generally employed when the affected joints or areas are limited to one or two sites. Dosage and frequency of injection varies depending on the condition and the site of injection. The usual dose is from 0.2 to 6 mg. The frequency usually ranges from once every three to five days to once every two to three weeks. Frequent intra-articular injection may result in damage to joint tissues.

Some of the usual single doses are:

Site of Injection	Amount of Dexamethasone Phosphate (mg)
Large Joints (e.g., Knee)	2 to 4
Small Joints (e.g., Interphalangeal, Temporomandibular)	0.8 to 1
Bursae	2 to 3
Tendon Sheaths	0.4 to 1
Soft Tissue Infiltration	2 to 6
Ganglia	1 to 2

Dexamethasone Sodium Phosphate http://www.drugs.com/pro/dexamethasone-sodium-phosphate.html
Injection is supplied as dexamethasone sodium phosphate in conjunction with some of the less soluble
esters for intra-articular and soft tissue injection.
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whenever the solution and container permit.

How is Dexamethasone Sodium Phosphate Supplied

Product No.	NDC No.	
16501	63323-165-01	Dexamethasone Sodium Phosphate Injection, USP (equivalent to 4 mg per mL dexamethasone phosphate) 1 mL fill, in a 2 mL flip-top vial, packaged in 25.
16505	63323-165-05	Dexamethasone Sodium Phosphate Injection, USP (equivalent to 20 mg/5 mL [4 mg/mL] dexamethasone phosphate) 5 mL fill, in a 5 mL flip-top vial, packaged in 25.
16530	63323-165-30	Dexamethasone Sodium Phosphate Injection, USP (equivalent to 120 mg per 30 mL [4 mg per mL] dexamethasone phosphate) 30 mL fill, in a 30 mL flip-top vial, packaged individually.

Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. Protect from freezing. Sensitive to heat. Do not autoclave.

Protect from light. Store container in carton until contents have been used.

Do not use if precipitate is present.

REFERENCES

1. Cavanagh, D.; Singh, K.B.: Endotoxin shock in pregnancy and abortion, in: "Corticosteroids in the Treatment of Shock", Schumer, W.; Nyhus, L.M., Editors, Urbana, University of Illinois Press, 1970, pp. 86-96.
2. Dietzman, R.H.; Ersek, R.A.; Bloch, J.M.; Lillehei, R.C.: High-output, low-resistance gram-negative septic shock in man, Angiology *20*: 691-700, Dec. 1969.
3. Frank, E.: Clinical observations in shock and management (In: Shields, T.F., ed.: Symposium on current concepts and management of shock), J. Maine Med. Ass. *59*: 195-200, Oct. 1968.
4. Oaks, W. W.; Cohen, H.E.: Endotoxin shock in the geriatric patient, Geriat. *22*: 120-130, Mar. 1967.
5. Schumer, W.; Nyhus, L.M.: Corticosteroid effect on biochemical parameters of human oligemic shock, Arch. Surg. *100*: 405-408, Apr. 1970.

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Revised: May 2014

PACKAGE LABEL - PRINCIPAL DISPLAY - Dexamethasone 1 mL Vial Label

NDC 63323-165-01 INTERNET ARCHIVE
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Dexamethasone Sodium Phosphate Injection, USP

equivalent to

4 mg per mL

Dexamethasone Phosphate

For IM or IV Use, See Insert For Other Routes

1 mL

Rx only

Sterile, Nonpyrogenic



PACKAGE LABEL - PRINCIPAL DISPLAY - Dexamethasone 1 mL Tray Label

NDC 63323-165-01

16501

Dexamethasone Sodium Phosphate Injection, USP

equivalent to

4 mg per mL

Dexamethasone Phosphate

For IM or IV Use, See Insert For Other Routes

1 mL

Rx only



Dexamethasone Sodium Phosphate

Dexamethasone Sodium Phosphate injection, solution

Product Information

Product Type	HUMAN PRESCRIPTION DRUG LABEL	**Item Code (Source)**	NDC:63323-165
Route of Administration	INTRAMUSCULAR, INTRAVENOUS	**DEA Schedule**	

Active Ingredient/Active Moiety
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Basis of Strength
Strength

Inactive Ingredients

Ingredient Name	Strength
SODIUM CITRATE	11 mg in 1 mL
SODIUM SULFITE	1 mg in 1 mL
BENZYL ALCOHOL	10 mg in 1 mL
SODIUM HYDROXIDE	
CITRIC ACID MONOHYDRATE	

Packaging

#	Item Code	Package Description
1	NDC:63323-165-01	25 VIAL in 1 TRAY
1		1 mL in 1 VIAL
2	NDC:63323-165-05	25 VIAL, MULTI-DOSE in 1 TRAY
2		5 mL in 1 VIAL, MULTI-DOSE
3	NDC:63323-165-30	1 VIAL, MULTI-DOSE in 1 BOX
3		30 mL in 1 VIAL, MULTI-DOSE

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA084916	09/07/2000	

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Establishment

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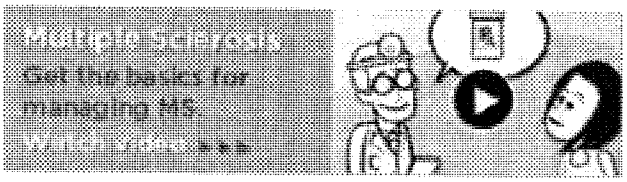
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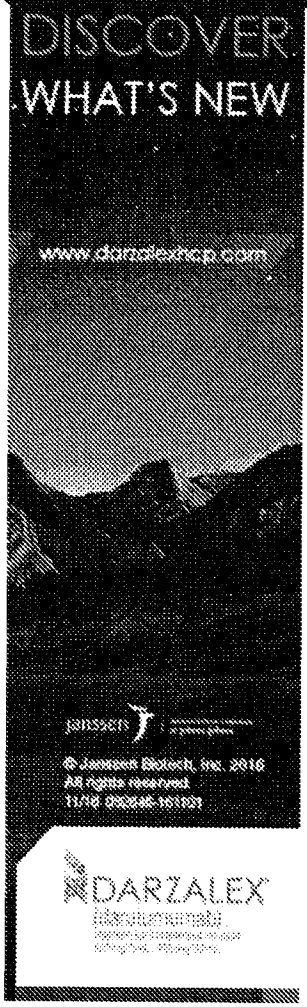
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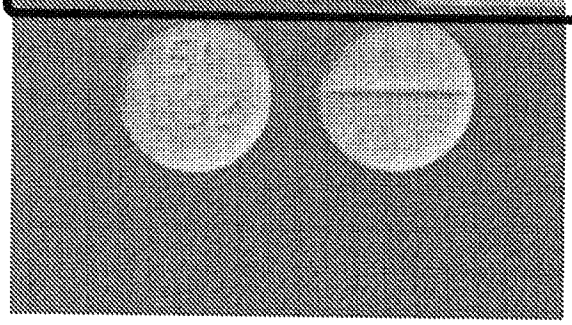
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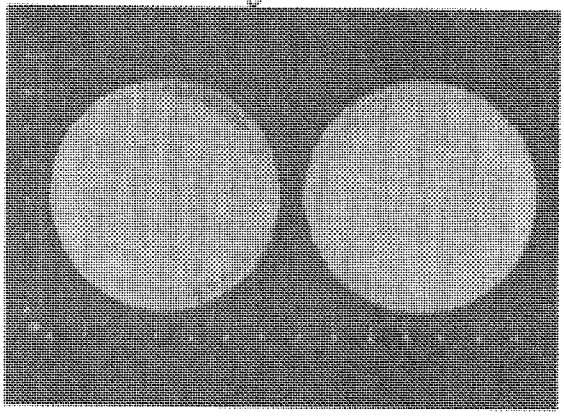
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Article

July 1983

Antiemetic Efficacy of Dexamethasone Therapy in Patients Receiving Cancer Chemotherapy

Peter A. Cassileth, MD; Edward J. Lusk, PhD; Susan Torri, RN; et al

Author Affiliations

Arch Intern Med. 1983;143(7):1347-1349. doi:10.1001/archinte.1983.00350070063012

Full Text

Abstract

• To assess the value of high-dose dexamethasone therapy in preventing the gastrointestinal (GI) side effects of chemotherapy, a randomized double-blind study was conducted in women receiving outpatient therapy for breast cancer. Single-dose dexamethasone sodium phosphate (10 mg) or placebo was administered intravenously in 57 trials in 22 women immediately before chemotherapy. Questionnaires (administered before therapy and 24 hours later) were compared for evidence of nausea, vomiting, and anorexia produced by chemotherapy. No GI Intolerance to chemotherapy was noted in 24 (83%) of the 29 dexamethasone trials *v* 16 (57%) of the 28 placebo trials. Dexamethasone trials produced the following results: no side effects in 50% (14/29), insomnia the night after chemotherapy in 21%

(6/29), an increase in energy levels in 24% (7/29), and an improvement in mood in 14% (4/29). High-dose dexamethasone therapy has useful application in alleviating the emetic effects of cancer chemotherapy.

(*Arch Intern Med* 1983;143:1347-1349)

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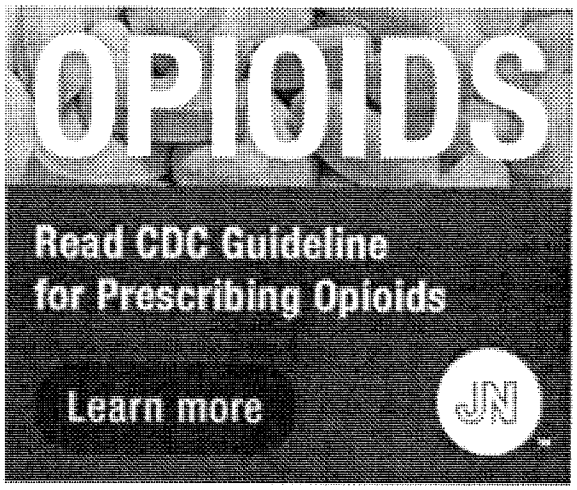
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Aprepitant

A Review of its Use in the Prevention of Nausea and Vomiting

Monique P. Curran and *Dean M. Robinson*

Wolters Kluwer Health | Adis, Auckland, New Zealand, an editorial office of Wolters Kluwer Health, Philadelphia, Pennsylvania, USA

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Data Selection

Sources: Medical literature published in any language since 1980 on 'aprepitant', identified using MEDLINE and EMBASE, supplemented by AdisBase (a proprietary database of Wolters Kluwer Health | Adis). Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: MEDLINE, EMBASE and AdisBase search terms were 'aprepitant' and ('chemotherapy-induced nausea and vomiting' or 'CINV') and ('postoperative nausea and vomiting' or 'PONV'). Searches were last updated 27 July 2009.

Selection: Studies in patients at risk of developing chemotherapy-induced or postoperative nausea and vomiting who had received aprepitant. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: Aprepitant, prevention of chemotherapy-induced nausea and vomiting, postoperative nausea and vomiting, pharmacodynamics, pharmacokinetics, therapeutic use, tolerability.

Contents

Summary 1854
1. Introduction 1856
2. Pharmacodynamic Properties 1856
3. Pharmacokinetic Properties 1857
   3.1 Absorption and Distribution 1857
   3.2 Metabolism and Elimination 1857
   3.3 Special Populations 1857
   3.4 Drug Interactions 1858
4. Therapeutic Efficacy 1858
   4.1 Chemotherapy-Induced Nausea and Vomiting (CINV) 1858
      4.1.1 Highly Emetogenic Chemotherapy 1860
      4.1.2 Moderately Emetogenic Chemotherapy 1863
      4.1.3 Special Populations 1865
   4.2 Postoperative Nausea and Vomiting (PONV) 1866
5. Pharmacoeconomic Considerations 1866
6. Tolerability 1868
   6.1 CINV 1868
      6.1.1 Highly Emetogenic Chemotherapy 1868

6.1.2 Moderately Emetogenic Chemotherapy 1869
6.2 PONV 1871
7. Dosage and Administration 1871
8. The Place of Aprepitant in the Prevention of Nausea and Vomiting 1872

Summary

Abstract

Aprepitant (Emend®) is a neurokinin-1 (NK_1) receptor antagonist that is able to alleviate the emetic effects of substance P. When combined with a standard regimen of a corticosteroid (dexamethasone) and a serotonin 5-HT_3 receptor antagonist (ondansetron), oral aprepitant (125 mg on day 1 then 80 mg once daily on days 2 and 3) was effective in the prevention of acute and delayed chemotherapy-induced nausea and vomiting (CINV) associated with single or multiple cycles of highly emetogenic chemotherapy (HEC). This aprepitant regimen was also effective in the prevention of CINV in patients treated with single or multiple cycles of moderately emetogenic chemotherapy (MEC). A single oral dose of aprepitant 40 mg administered prior to patients undergoing abdominal surgery was also effective in the prevention of postoperative nausea and vomiting (PONV). Aprepitant was generally well tolerated. Aprepitant is a recommended option for the treatment of PONV, and when combined with a corticosteroid and 5-HT_3 receptor antagonist is a recommended regimen for the treatment of CINV.

Pharmacological Properties

Aprepitant is a selective, high-affinity antagonist at human NK_1 receptors and is consequently able to alleviate the emetic effects of substance P. Aprepitant has little or no affinity for serotonin 5-HT_3, dopamine or corticosteroid receptors. Aprepitant crosses the blood-brain barrier. Aprepitant had no effect on gastrointestinal motor function in healthy volunteers.

The pharmacokinetics of aprepitant are nonlinear across the recommended dose range, with clearance and absolute bioavailability decreasing with increasing dose. Following administration of a single oral dose of aprepitant 40 mg (recommended dosage in the prevention of PONV) to healthy volunteers, the area under the plasma concentration-time curve (AUC) from time zero to infinity was 7.8 μg • h/mL and the maximum plasma concentration (C_{max}) was 0.7 μg/mL. The median time to C_{max} (t_{max}) was ≈3.0 hours. Following administration of oral aprepitant 125 mg on day 1 followed by 80 mg once daily on days 2 and 3 (recommended dosage in the prevention of CINV) to healthy volunteers, the AUC from 0 to 24 hours, the C_{max} and t_{max} were 19.6 μg • h/mL, 1.6 μg/mL and ≈4 hours, respectively, on day 1 and 21.2 μg • h/mL, 1.4 μg/mL and ≈4 hours, respectively, on day 3. Aprepitant is excreted largely as metabolites in the urine and via biliary excretion in the faeces. The apparent terminal half-life was 9–13 hours.

Since aprepitant is metabolized by cytochrome P450 (CYP) 3A4, coadministration of aprepitant and inhibitors or inducers of this isoenzyme will induce changes in the plasma levels of aprepitant. As a moderate inhibitor of CYP3A4, aprepitant can increase plasma concentrations of coadministered substances that are metabolized through CYP3A4. As a moderate inducer of CYP2C9 and a mild inducer of CYP3A4, aprepitant can decrease plasma concentrations of substrates metabolized by these isoenzymes.

Therapeutic Efficacy

In phase III studies in patients with solid tumours treated with a single cycle of HEC, an aprepitant regimen (containing aprepitant 125 mg on day 1 then 80 mg once daily on days 2 and 3 plus dexamethasone and ondansetron) resulted in significantly higher complete response (no emesis and no rescue therapy) rates than with the

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control regimen of ondansetron plus dexamethasone (63–73% vs 43–61%; p < 0.01) during the overall (day 1–5) phase after HEC administration. Complete response rates during the acute phase (day 1; 83–89% vs 68–79%) and the delayed phase (days 2–5; 68–75% vs 47–63%) were also significantly higher with the aprepitant than with the control regimen. In particular, the rate of no emesis was significantly higher with the aprepitant than the control regimen during the acute, delayed and overall phases. In a multiple-cycle extension study in which patients received of up to five additional cycles of HEC, the efficacy of the aprepitant regimen was maintained throughout each of the multiple cycles.

In patients with breast cancer treated with MEC (cyclophosphamide ± anthracycline), an aprepitant regimen (aprepitant plus dexamethasone plus ondansetron), compared with a control regimen (dexamethasone plus ondansetron) resulted in more patients achieving a complete response during the overall phase (51% vs 42%; p = 0.015), according to data from a large phase III trial. The between-group difference in complete response rates was primarily driven by the rate of no emesis (76% vs 59%; unadjusted p-value < 0.001), with no significant between-group difference for the use of rescue medication. In a multiple-cycle extension of this trial, the advantage of the antiemetic effect of the aprepitant regimen over the control regimen seen in the first cycle was maintained throughout the additional three cycles of MEC. In a large phase III trial in patients with a variety of malignancies receiving MEC, significantly more recipients of a single cycle of an aprepitant than a control regimen had no emesis (76% vs 62%; p < 0.001) and a complete response (69% vs 56%; p < 0.001) during the overall phase.

An aprepitant regimen compared with a control regimen was considered to be cost-effective with regard to the cost per QALY in the prevention of CINV in two European studies, although not according to a US analysis.

Although a large phase III trial failed to prove that a single dose of oral aprepitant 40 mg was superior to ondansetron in preventing PONV (as measured by the proportion of patients with complete response in the 24 hours after surgery), a second phase III trial of similar design established that a single dose of aprepitant 40 mg was noninferior to ondansetron, with 64% versus 55% of patients achieving a complete response. Aprepitant was significantly more effective than ondansetron at preventing vomiting in the 24 and 48 hours after surgery in both studies (p < 0.001).

Tolerability

An antiemetic regimen containing dexamethasone, ondansetron and aprepitant (administered administered orally as a single 125 mg dose on day 1 and then 80 mg once daily on days 2 and 3) was generally well tolerated when used in the prevention of CINV in cancer patients receiving single or multiple cycles of HEC or MEC. The incidence of adverse events in recipients of an aprepitant regimen was similar to that in recipients of the control regimen (dexamethasone plus ondansetron). Commonly reported adverse events (≥10% of recipients) were asthenia/fatigue, nausea, hiccups, constipation, diarrhoea and anorexia. Laboratory adverse events (≥3% of recipients) included proteinuria and increases in ALT, AST, blood urea nitrogen and serum creatinine. The adverse event profile of an aprepitant regimen in patients receiving MEC was generally similar to that reported in patients receiving HEC.

The tolerability profile of a single oral dose of aprepitant 40 mg when used in the prevention of PONV was similar to that of a single intravenous dose of ondansetron in patients undergoing open, abdominal surgery who participated in two, large, well controlled studies. Most adverse events were mild to moderate in intensity. Commonly reported adverse events (≥5% of recipients of either treatment group) were constipation, nausea, pruritus, pyrexia, hypotension, headache and flatulence.

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1. Introduction

Nausea and vomiting are common adverse events experienced by patients following chemotherapy or surgery.[1-4] Poorly controlled chemotherapy-induced nausea and vomiting (CINV) or postoperative nausea and vomiting (PONV) can lead to dehydration, malnutrition and electrolyte imbalance, and may be associated with a variety of complications including oesophageal tears, declining behavioural and mental status, and wound dehiscence. These symptoms can result in a reduced willingness of the patient to be treated in the future or delays in discharge from hospital.

PONV can occur in as many as 79% of patients,[3] while approximately 70–80% of all cancer patients receiving chemotherapy experience nausea and/or vomiting, with 10–40% of cancer patients experiencing anticipatory nausea and/or vomiting.[4] The incidence and severity of CINV are affected by a number of factors including the chemotherapy involved, the dosage of the chemotherapy, the schedule and route of administration of the chemotherapy and patient-related factors such as age, sex and history of alcohol use.[4]

Nausea and/or vomiting induced by chemotherapy are commonly classified as acute, delayed, anticipatory, breakthrough and refractory (table I).

Vomiting results from the stimulation of a multistep reflex pathway controlled in the brain.[2] Vomiting is triggered when afferent impulses travel from the chemoreceptive trigger zone, the pharynx, the gastrointestinal (GI) tract and the cerebral cortex to the vomiting centre in the brain (located in the medulla). Efferent impulses then travel from the vomiting centre to the salivation centre, abdominal muscles, respiratory centre and cranial nerves causing vomiting.

Table I. Types of chemotherapy-induced nausea and/or vomiting

Acute	Occurs within a few minutes to several hours after chemotherapy and usually resolves within 24 hours
Delayed	Occurs more than 24 hours after chemotherapy
Anticipatory	Occurs before a cycle of chemotherapy. A conditioned response
Breakthrough	Occurs despite prophylactic treatment and/or requires rescue antiemetic agents
Refractory	Occurs during subsequent treatment cycles when antiemetic prophylaxis and/or rescue have failed in earlier cycles

Agents that have been used in the prevention of vomiting are those that block neurotransmitter receptors in the CNS and GI tract that mediate the afferent inputs, and include serotonin 5-HT_3 receptor antagonists, corticosteroids, dopamine receptor antagonists and neurokinin-1 (NK_1) receptor antagonists. Since no single agent can be expected to provide complete protection against the various phases of emesis, a combination of antiemetic agents are usually administered.

Aprepitant (Emend®) is a selective, high-affinity NK_1 receptor antagonist that blocks the binding of substance P.[5] This review examines the pharmacological properties, therapeutic efficacy, pharmacoeconomics and tolerability of orally administered aprepitant in the prevention of PONV in surgical patients, and in the prevention of CINV in cancer patients treated with highly emetogenic chemotherapy (HEC) or moderately emetogenic chemotherapy (MEC).

2. Pharmacodynamic Properties

The pharmacodynamic properties of aprepitant have been reviewed previously;[5] therefore, only a brief summary is provided herein.

Aprepitant selectively, and with high affinity, blocks the binding of substance P at NK_1 receptors in the CNS;[6] *in vitro*, the aprepitant concentration that displaced 50% of substance P from the NK_1 receptors was 0.12 nmol/L.[7]

Aprepitant had low affinity for NK_2 and NK_3 receptors. It had little or no affinity for the serotonin 5-HT_3, dopamine or corticosteroid receptors (other neurotransmitters involved in the control of emesis).[6]

In vivo and human positron emission tomography studies demonstrate that aprepitant crosses the blood-brain barrier and occupies brain NK_1 receptors.[7-9] A 125 mg dose of aprepitant resulted in ≥90% occupancy of NK_1 receptors in the CNS.[9]

Aprepitant displayed acute- and delayed-phase antiemetic effects in cisplatin-induced emesis in animal models[6,7,10,11] and augments

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the antiemetic effect of the corticosteroid dexamethasone or the 5-HT_3 receptor antagonist ondansetron in animal[11] and human studies (see section 4).

Aprepitant had no effect on GI motor function in healthy volunteers.[12]

3. Pharmacokinetic Properties

Data in this section have largely been obtained from the US[6] and European[13] prescribing information.

3.1 Absorption and Distribution

Following administration of a single oral dose of aprepitant 40 mg (recommended dosage in the prevention of PONV; see section 7) in the fasted state, the area under the plasma concentration-time curve (AUC) from time zero to infinity was 7.8 μg • h/mL and the maximum plasma concentration (C_{max}) was 0.7 μg/mL.[6] The median time to C_{max} was ≈3.0 hours. Administration of a single dose of aprepitant 40 mg with a standard breakfast decreased the aprepitant C_{max} by 18% but did not affect AUC.[13] The decrease in C_{max} was not considered to be clinically relevant.

The pharmacokinetic profile of oral aprepitant administered as a single dose of 125 mg on day 1 followed by 80 mg once daily on days 2 and 3 (recommended dosage for the prevention of CINV; see section 7) to healthy volunteers is shown in table II.[6,13] The mean absolute oral bioavailability of aprepitant decreased with increasing dose; after doses of 80 and 125 mg under fasting conditions was 67% and 59%.[13] Food had no clinically meaningful effect on the bioavailability of aprepitant.[6,13]

Total protein binding of aprepitant is >95% and the mean apparent volume of distribution at steady state is ≈70 L.[6] Aprepitant crosses the blood-brain barrier in humans and the placenta in animal studies.[6]

Table II. Pharmacokinetic parameters of oral aprepitant when administered as a single 125 mg dose on day 1 followed by 80 mg once daily on days 2 and 3.[6,13] Twelve healthy volunteers were enrolled in the open-label study

Pharmacokinetic parameters	Day 1	Day 3
Mean C_{max} (μg/mL)	1.6	1.4
Mean AUC_{24} (μg • h/mL)	19.6	21.2
Median t_{max} (h)	≈4	≈4
Mean $t_{½β}$ (h)		≈9–13

AUC_{24} = area under the concentration-time curve from time 0 to 24 hours; C_{max} = maximum plasma concentration; t_{max} = time to C_{max}; $t_{½β}$ = elimination half-life.

3.2 Metabolism and Elimination

Aprepitant undergoes extensive metabolism.[6,13] Metabolism occurs largely as a result of oxidation at the morpholine ring and its side chain.[14] Seven weakly active metabolites have been identified. *In vitro* studies using human liver microsomes suggested that mainly cytochrome P450 (CYP) 3A4 and to a lesser extent CYP1A2 and CYP2C19 (but not CYP2D6, CYP2C9 or CYP2E1) were involved in the metabolism of aprepitant.[6,15] The unchanged drug accounted for ≈24% of the radioactivity in the plasma following administration of a single oral dose of [^{14}C]-aprepitant to healthy volunteers.[6]

Aprepitant is excreted largely as metabolites in the urine and via biliary excretion in the faeces.[6,13] After a single 100 mg intravenous dose of a prodrug of [^{14}C]-aprepitant to healthy volunteers, 57% of the radioactivity was detected in the urine and 45% in the faeces. The apparent plasma clearance was dose dependent, decreasing with increasing dose and was ≈62–90 mL/min and the apparent terminal elimination half-life was ≈9–13 hours.[6]

3.3 Special Populations

The pharmacokinetic profile of a 3-day regimen of aprepitant (125 mg on day 1 and then 80 mg/day on days 2 and 3) in 17 adolescent cancer patients[16] was similar to that in 12 healthy adult patients (data obtained from a previous study[17]). There are no clinically significant differences in the pharmacokinetics of aprepitant between male and female patients, between races (White, Black and Hispanic), between patients aged ≥65 years and those aged <65 years, and between healthy volunteers and patients with mild to moderate hepatic insufficiency, those with severe renal insufficiency or those requiring

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haemodialysis.[6,13,18] In these patients, no dosage adjustment is necessary. No data are available regarding the pharmacokinetics in patients with severe hepatic insufficiency.

3.4 Drug Interactions

Aprepitant is a substrate and dose-dependent inhibitor of CYP3A4, and an inducer of CYP3A4, CYP2C9 and potentially other isoenzymes.[6,13,15]

Since aprepitant is metabolized by CYP3A4, coadministration of aprepitant and inhibitors or inducers of this isoenzyme will induce changes in the plasma levels of aprepitant (table III).[6,13] Consequently, drugs such as ketoconazole, itraconazole, nefazodone, troleandomycin, clarithromycin, ritonavir and nelfinavir, which are strong inhibitors of CYP3A4, should be avoided as they may result in increased plasma concentrations of aprepitant. Moderate inhibitors of CYP3A4 (e.g. diltiazem) should be administered with caution. Agents that strongly induce CYP3A4 activity (e.g. rifampicin [rifampin], carbamazepine, phenytoin) may decrease the plasma level of aprepitant and should be avoided.[13]

As a moderate inhibitor of CYP3A4, a 3-day regimen of aprepitant (125 mg on day 1 and then 80 mg/day on days 2 and 3) may increase plasma concentrations of coadministered substances that are metabolized by CYP3A4 (table III). A single dose of aprepitant 40 mg is not expected to increase the plasma concentrations of agents that are metabolized by CYP3A4. Aprepitant should not be used concurrently with pimozide, terfenadine, astemizole or cisapride.[6,13] Docetaxel, paclitaxel, etoposide, irinotecan, ifosfamide, imatinib, vinorelbine and vincristine are agents that are metabolized by CYP3A4. However, there was no significant change in the pharmacokinetic parameters of docetaxel[23] or vinorelbine[24] when these agents were coadministered with a 3-day aprepitant regimen (table III). Nevertheless, careful monitoring is advised when aprepitant is coadministered with any chemotherapeutic agent that is metabolized by CYP3A4. The corticosteroids dexamethasone and methylprednisolone are substrates of CYP3A4 and their plasma levels are increased when coadministered with aprepitant (table III). Therefore, it is recommended that the usual oral dexamethasone dosage should be reduced by approximately 50%, the usual intravenous methylprednisolone dosage should be reduced by approximately 25%, and the usual oral methylprednisolone dosage should be reduced by approximately 50% when coadministered with a 3-day regimen of aprepitant.[6,13]

Because aprepitant has been shown to induce CYP2C9, coadministration of aprepitant with agents that are known to be metabolized by CYP2C9, such as warfarin, tolbutamide and phenytoin, may result in lower plasma concentrations of these agents (table III); therefore, caution is advised.[6,13]

Aprepitant reduced the plasma levels of coadministered oral hormonal contraceptives (table III); therefore, the efficacy of oral contraceptives may be reduced. Alternative or back-up methods of contraception are advised for 1 month following the last dose of aprepitant.[6,13]

4. Therapeutic Efficacy

This section focuses on the efficacy of aprepitant when used as part of an antiemetic regimen in the prevention of CINV in adult or adolescent cancer patients (section 4.1) and when used as monotherapy in the prevention of PONV in adult surgical patients (section 4.2). The endpoints used in these trials are shown in table IV.

4.1 Chemotherapy-Induced Nausea and Vomiting (CINV)

The efficacy of aprepitant in the prevention of CINV has been evaluated in adult patients receiving HEC (section 4.1.1) or MEC (section 4.1.2) and in adolescent patients receiving emetogenic chemotherapy (section 4.1.3). Focus will be on phase III trials in which aprepitant was administered as part of an antiemetic regimen that also included a corticosteroid (dexamethasone) and a serotonin 5-HT_3 receptor antagonist (ondansetron). Aprepitant was administered orally as a single 125 mg dose on day 1 and then 80 mg once daily on days 2 and 3. Specific details of the regimens and the

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Table III. Drug interactions involving aprepitant. Agents were administered orally in healthy volunteers unless otherwise stated

Agent	Dose of aprepitant (mg) [day(s) administered]	Dosage of concomitant agent (mg[a]) [day(s) administered]	Clinically meaningful pharmacokinetics effects	
			aprepitant	concomitant agent
Antiemetics				
Dexamethasone (CYP3A4 substrate)[6,13,19]	125 [1] then 80 [2–5]	20 [1] then 8 [2–5]	None	↑ AUC 2.2-fold (day 1 and 5)
Granisetron[20]	125 [1] then 80 [2, 3]	2 [1]	None	None
Methylprednisolone (CYP3A4 substrate)[6,13,19]	125 [1] then 80 [2, 3]	125 IV [1] then 40 [2, 3]	None	↑ AUC 1.34-fold (day 1) and 2.5-fold (day 3)
Ondansetron (IV)[20]	375 [1] then 250 [2–5]	32 [1]	None	None
Palonosetron (IV)[21]	125 [1] then 80 [2, 3]	0.25 [1]	None	None
Chemotherapeutic agents				
Cyclophosphamide[22]	125 [1] then 80 [2, 3]	Recommended regimen		None
Docetaxel[23]	125 [1] then 80 [2, 3]	Recommended regimen	None	None
Vinorelbine[24]	125 [1] then 80 [2, 3]	Recommended regimen	None	None
CYP3A4 inhibitors				
Diltiazem[6,15]	230[b] [1–5]	360 [1–5]	↑ AUC 2-fold	↑ AUC 1.7-fold
Ketoconazole[6,13,15]	125 [1]	400 [1–10]	↑ AUC ≈5-fold ↑ $t_{1/2}$ 3-fold	None
CYP3A4 inducer				
Rifampicin[6,13]	375 [9]	600 [1–14]	↓ AUC 11-fold ↓ $t_{1/2}$ 3-fold	None
CYP3A4 substrates				
Midazolam[6,13]	125 [1] then 80 [2–5]	2 [1 and 5]	None	↑ AUC 2.3-fold (day 1) and 3.3-fold (day 5)
Midazolam (IV)[6,13]	125 [1] then 80 [2,3]	2 [0, 4, 8, 15]	None	↑ AUC 25% (day 4) and ↓19% (day 8)
Midazolam[6]	40 [1]	2 [1]	None	↑ AUC 1.2-fold (day 1)
CYP2C9 substrates				
Tolbutamide[6,13]	125 [1] then 80 [2, 3]	500 [0, 4, 8, 15]	None	↓ AUC by 23%, 28% and 15% on days 4, 8 and 15
Warfarin[6,13,17]	125 [1] then 80 [2, 3]	Titrated to stable INR	None	↓ C_{min} of S-warfarin by 34% (day 8) ↓ INR by 14% (day 5)
CYP2D6 substrate				
Paroxetine[6,13]	85 or 170[b]	20 [1–14]	↓ AUC ≈25% ↓ C_{max} ≈20%	↓ AUC ≈25% ↓ C_{max} ≈20%
Other agents				
Digoxin[25]	125 [7] then 80 [8–11]	0.25 [1–13]	None	None
Oral contraceptives[6,13]	100 [1–14]	EE 35 μg [1–21] NOR 1 [1–21]	None	↓ AUC of EE by 43% ↓ AUC of NOR by 8%
	125 [1] then 80 [2, 3]	EE [1–21] NOR [1–21]		↓ AUC of EE by 19% (day 10) ↓ C_{min} of EE by ≤84% (days 9–21) ↓ C_{min} of NOR by ≤60%

a Unless otherwise stated.

b Administered in tablet form once daily; dosage comparable to capsule formulation stated.

AUC = area under the concentration-time curve; C_{max} = maximum plasma concentration; C_{min} = trough plasma concentrations; **CYP** = cytochrome P450; **EE** = ethinyl estradiol; **INR** = International Normalized Ratio; **IV** = intravenous; **NOR** = norethisterone (norethindrone); $t_{1/2}$ = elimination half-life; ↓ indicates decreases; ↑ indicates increases.

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Table IV. Efficacy endpoints for randomized, double-blind, phase III trials involving aprepitant regimens used in the prevention of nausea and vomiting in patients receiving chemotherapy or postoperatively in patients who have undergone surgery

Endpoint	Definition
No emesis	No vomiting (oral expulsion of stomach contents), retching or dry heaves (an attempt to vomit that is not productive of stomach contents) regardless of use of rescue medication
No rescue therapy	No use of medication to treat established nausea or emesis
No nausea	Maximum nausea VAS rating <5 mm
No significant nausea	Maximum nausea VAS rating <25 mm
Complete response	No emesis (or no vomiting) and no rescue therapy
Complete protection	No emesis (or no vomiting), no rescue therapy, no significant nausea
The impact of CINV on daily life	FLIE[29] total score >108 out of a maximum possible score of 126

CINV = chemotherapy-induced nausea and vomiting; FLIE = Functional Living Index Emesis; VAS = visual analog scale from 0 ('no nausea') to 100 mm ('worst possible nausea').

dosage of each of the other antiemetic agents involved in the trials are presented in table V (HEC) and table VI (MEC).

The efficacy of an aprepitant-containing regimen was assessed during the acute (0–24 hours), delayed (25–120 hours) and overall (0–120 hours) phases after the administration of HEC or MEC. The primary endpoint in these studies was generally the overall complete response rate (table IV). The primary analysis generally involved the modified intent-to-treat (mITT) population (patients who received chemotherapy, at least one dose of the study drug and had at least one post-treatment assessment during cycle 1).

4.1.1 Highly Emetogenic Chemotherapy

Dose-ranging, phase II studies demonstrated the efficacy of aprepitant when added to a standard antiemetic regimen (corticosteroid plus a 5-HT_3 receptor antagonist) in the prevention of CINV during single[33] or multiple[34] cycles of cisplatin-based HEC. The phase II trials supported the use of the corticosteroid dexamethasone for the control of acute emesis and demonstrated the need to lower the dosage of dexamethasone in order to compensate for the inhibition of its metabolism by aprepitant (see section 3.4). Since the first emetic episodes occurred within the first 3 days of cisplatin administration, and given the relatively long half-life of aprepitant (see section 3), aprepitant was administered over 3 days in the subsequent phase III trials.

Three randomized, double-blind, multicentre, phase III trials assessed the efficacy of aprepitant in combination with dexamethasone and ondansetron in the prevention of CINV in adult patients treated with a single cycle of cisplatin-based HEC.[27-29] Two trials (one conducted primarily in the US and EU[27] and the other conducted only in Latin America[28]) were designed to be identical to allow the subsequent pooling and analysis of data.[35-38]

Patients (n = 530,[27] 569[28] and 489[29]) scheduled to receive cisplatin ≥70 mg/m^2 were randomized to treatment with either an aprepitant regimen (aprepitant plus dexamethasone plus ondansetron) or a control regimen (dexamethasone plus ondansetron; table V). In two of the trials,[27,28] ondansetron was administered intravenously on day 1 only (table V). In the third phase III trial,[29] ondansetron was administered intravenously on day 1 and then orally on days 2–4 (table V).

Patients (n = 851) who had completed a single cycle of HEC from the two identical phase III trials[27,28] continued in a multiple-cycle, double-blind, extension study in which patients were treated with up to an additional five cycles of HEC.[36]

Additional antiemetic agents were not permitted within 2 days prior to cisplatin adminis-

Table V. Aprepitant (APR) or control (CON) regimens used in phase III trials in patients treated with highly emetogenic chemotherapy

Regimen	Dose (mg) [day(s) administered]
APR[27-29]	APR 125 [1] PO[a] then 80 od [2, 3] PO
	DEX 12 [1] PO[b] then 8 od [2–4] PO
	OND 32 [1] IV
CON[27,28]	DEX 20 [1] PO[b] then 8 bid [2–4] PO
	OND 32 [1] IV
CON[29]	DEX 20 [1] PO[b] then 8 bid [2–4] PO
	OND 32 [1] IV then 8 bid [2–4] PO

a Administered 1 h prior to chemotherapy.

b Administered 30 min prior to chemotherapy.

bid = twice daily; DEX = dexamethasone; IV = intravenously; od = once daily; OND = ondansetron; PO = orally.

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Table VI. Aprepitant (APR) or control (CON) regimens used in phase III trials in patients treated with moderately emetogenic chemotherapy. All agents were administered orally

Regimen	Dose (mg) [day(s) administered]
APR[30-32]	APR 125 [1][a] then 80 od [2, 3] DEX 12 [1][b] OND 8 bid [1]
CON[30-32]	DEX 20 [1][b] OND 8 bid [1–3]

a Administered 1 h prior to chemotherapy.

b Administered 30 minutes prior to chemotherapy.

bid = twice daily; **DEX** = dexamethasone; **od** = once daily; **OND** = ondansetron.

tration (day 1) or between days 1–6 (except as rescue medication for established nausea or vomiting). Additional HEC (Hesketh level ≥3) was permitted only on day 1 and was administered to 10–17% of patients.[27-29] Concomitant therapy administered in addition to cisplatin included etoposide, fluorouracil, gemcitabine, vinorelbine, paclitaxel, cyclophosphamide, doxorubicin and docetaxel.[6]

Patients included in the studies were cisplatin-naive, aged ≥18 years, with solid tumours confirmed by histology, a Karnofsky score ≥60 and a life expectancy greater ≥3 months. Exclusion criteria included abnormal laboratory values (for platelets, absolute neutrophils, AST, ALT, bilirubin or creatinine), a planned multiple-day, cisplatin-based chemotherapy regimen in a single cycle, MEC or HEC in the 6 days prior to and/or after the day of cisplatin administration, radiation therapy to the abdomen or pelvis within 1 week before HEC administration or on days 1–6 after HEC.[27-29]

Single-Cycle Chemotherapy

Phase III studies in patients with solid tumours treated with a single cycle of HEC demonstrated that a regimen containing aprepitant plus dexamethasone plus ondansetron resulted in significantly more patients with an overall complete response (primary endpoint) than with the control regimen of dexamethasone plus ondansetron alone (63–73% vs 43–61%; $p < 0.01$ for all comparisons; table VII).[27-29] Complete response rates during the acute (83–89% vs 68–79%) and delayed (68–75% vs 47–63%) phases were also significantly higher with the aprepitant than with the control regimen (see table VII for p-values).

A combined analysis[38] of the two identical phase III trials[27,28] indicated that the aprepitant regimen provided greater overall complete response than the control regimen irrespective of sex (women 66% vs 41%, $p < 0.001$; men 69% vs 53%, $p < 0.001$).

Significantly more patients treated with the aprepitant than the control regimen had no emesis during the acute, delayed and overall phases (table VII), according to data from all three trials.[27-29] Moreover, Kaplan-Meier analysis indicated that the time to the first emesis after the initiation of HEC was longer with the aprepitant regimen than the control regimen ($p < 0.001$; based on the log-rank test).[27-29] Combined data from the two identical studies indicated the difference between the two groups on the Kaplan-Meier curves began at approximately 12–16 hours after HEC administration (statistical analyses not reported).[39] Similarly, in the third study,[29] the Kaplan-Meier curves for each of the treatment regimens began to visually separate at 10 hours, with the between-group difference being significant after 21 hours ($p < 0.05$; backwards log-rank procedure).

According to a combined analysis[35] of the two identical phase III trials,[27,28] delayed emesis was correlated with, but not entirely dependent upon, the presence of acute emesis. Across both studies, acute emesis occurred in 13% of recipients of the aprepitant regimen and 26% of recipients of the control regimen ($p < 0.01$). Of these patients, the incidence of subsequent delayed emesis was 17% lower with the aprepitant compared with the control regimen. Of the patients who did not experience acute emesis, the incidence of delayed emesis was 16% less with aprepitant than with the control. Thus, it was concluded by the researchers that aprepitant conferred a similar degree of improvement in delayed phase protection, irrespective of acute emesis. They concluded that the decrease in delayed emesis could not be attributed to a 'carry over' effect that resulted from a decrease in acute emesis.

The effect of aprepitant on nausea was not as apparent as its effect on emesis. In one study,[28] there was a significant difference between the

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Table VII. Clinical efficacy of an oral aprepitant (APR) antiemetic regimen in patients (pts) receiving one cycle of highly emetogenic cisplatin-based chemotherapy[a] in randomized, double-blind, multicentre, phase III trials.[27-29] Data have also been obtained from the aprepitant manufacturer's US prescribing information[8] and the EU summary of product characteristics.[13] Pts were randomized to an APR (APR plus dexamethasone plus ondansetron) or a control (CON) regimen (dexamethasone plus ondansetron; see table V for further dosage and administration details). Placebo tablets/capsules were administered to maintain blinding. Endpoints were assessed during the acute (day 1), delayed (days 2–5) or overall (days 1–5) phases after chemotherapy. Analyses were performed on the modified intent-to-treat population[b]

Study	Regimen (pt no.)	Phase	Endpoint[c] (% pts)					
			complete response	complete protection	no emesis	no nausea	no significant nausea	no rescue medication
Hesketh et al.[27]	APR	Acute	89***	85**	90**	72[d]	91[d]	94*
	(260)	Delayed	75***	66**	81**	51	75	81*
		Overall	73***[e]	63**	78**	48	73	81**
	CON	Acute	78	75	79	69[d]	87[d]	89
	(261)	Delayed	56	52	59	48	69	74
		Overall	52[e]	49	55	44	66	71
Poli-Bigelli et al.[28]	APR	Acute	83***	80**	84**			96**
	(261)[f]	Delayed	68***	61**	72**	53**	73	83*
		Overall	63***[e]	56**	66**	49*	71	82**
	CON	Acute	68	65	69			90
	(263)	Delayed	47	44	48	40	65	74
		Overall	43[e]	41[e]	44	39	64	73
Schmoll et al.[29]	APR	Acute	88**		89**		92	94
	(243)	Delayed	74**		79***		76	84
		Overall	72**[e]		77**[e]		73	82
	CON	Acute	79		81		90	93
	(241)	Delayed	63		64		72	82
		Overall	61[e]		62[e]		70	80

a Pts received a single dose of intravenous cisplatin ≥70 mg/m² on day 1 of cycle 1.

b Pts who received chemotherapy and at least one dose of the study drug and had at least one post-treatment assessment during cycle 1.

c See table IV for definition of endpoints.

d Statistical analysis not performed.

e Primary endpoint.

f There were 261 pts in the acute phase and 260 pts in the delayed and overall phases.

* $p<0.05$, ** $p<0.01$, *** $p<0.001$ vs CON.

aprepitant and control regimen in the number of patients with no nausea in the delayed and overall phases (table VII). There was no between-group difference in the number of patients with no significant nausea in any of the three studies.[27-29]

The number of patients requiring rescue medication was significantly lower in recipients of the aprepitant regimen than the control regimen during all phases after chemotherapy in two[27,28] of the three[27-29] trials (table VII).

Two studies assessed the impact of CINV on daily life, according to the total score on the Functional Living Index Emesis (FLIE) questionnaire (see table IV for further explanation of this endpoint).[27,28] Significantly more recipients of the aprepitant than the control regimen experienced minimal or no impact of CINV on daily living, according to data from the two individual studies (75% vs 64%[28] and 74% vs 64%;[27] statistical analyses not reported) or from a combined analysis of the two studies (74% vs 64%; $p<0.01$; analysis not adjusted for multiplicity).[35]

Multiple-Cycle Chemotherapy

In patients who continued into the multiple-cycle extension study,[36] the efficacy of the aprepitant regimen was maintained throughout each of the multiple HEC cycles (up to five additional

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cycles; see figure 1). In every cycle, the estimated probability of no emesis and no significant nausea over the 5 days after HEC administration was significantly higher with the aprepitant than the control regimen (see figure 1).

4.1.2 Moderately Emetogenic Chemotherapy

Randomized, double-blind, multicentre, phase III trials assessed the efficacy of aprepitant in combination with dexamethasone and ondansetron in the prevention of CINV in adult patients with breast cancer[30] or various malignancies[31] who were treated with a single cycle of MEC.

Patients (n = 866[30] and 848[31]) were randomized to treatment with an aprepitant (aprepitant plus dexamethasone plus ondansetron) regimen or a control (dexamethasone plus ondansetron) regimen (see table VI for further details). In addition, patients (n = 744) who had completed one cycle of MEC from one of these trials[30] entered a double-blind, multiple-extension study during which they received up to three additional cycles of MEC.[40] A smaller, double-blind, single-centre study also randomized 127 Chinese patients receiving MEC to an aprepitant or control regimen (table VI).[32] All agents were administered orally.

Eligible patients were aged ≥18 years of age, naive to MEC or HEC, had histologically confirmed breast cancer[30,32] or any histologically or cytologically confirmed malignant disease[31] requiring treatment with non-cisplatin-based MEC, Karnofsky scores ≥60 and a predicted life expectancy of ≥4 months. Exclusion criteria included a symptomatic, CNS malignancy, vomiting in the 24 hours prior to treatment, abnormal laboratory values (platelets, absolute neutrophils, AST, ALT, bilirubin or creatinine), planned cisplatin-based chemotherapy, MEC or HEC in the week prior to treatment, radiation therapy to the abdomen or pelvis within 1 week of treatment and up to 6 days after treatment, or systemic corticosteroid use.

In the studies in patients with breast cancer,[30,32] patients were scheduled for treatment with intravenous cyclophosphamide 750–1500 mg/m^2 monotherapy, or intravenous cyclophosphamide 500–1500 mg/m^2 plus intravenous doxorubicin ≤60 mg/m^2 or epirubicin ≤100 mg/m^2.

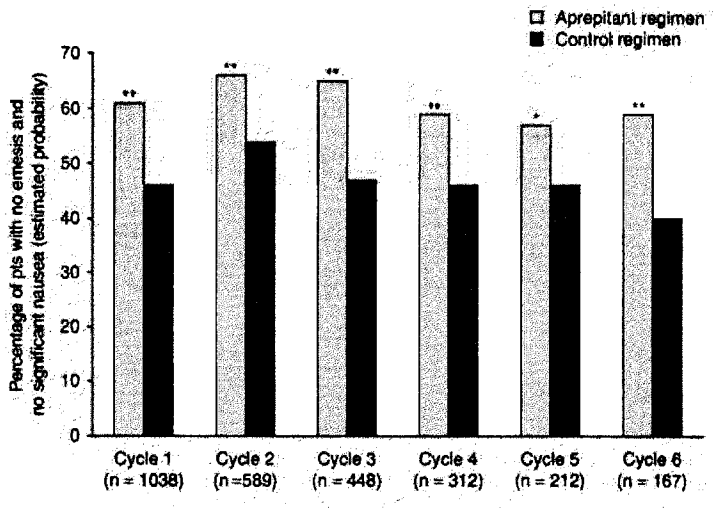


Fig. 1. Estimated probability of overall rate of cancer patients (pts) with no emesis and no significant nausea after treatment with an aprepitant (aprepitant plus dexamethasone plus ondansetron) or control (dexamethasone plus ondansetron) regimen in the 5 days after administration of highly emetogenic, cisplatin-based chemotherapy (HEC). Pooled data[36] from the multiple-cycle extensions of two randomized, double-blind, multicentre studies.[27,28] Pts received an aprepitant or control regimen (see table V for details of dosage) for up to an additional five cycles of HEC. Analyses are based on the modified intent-to-treat population and used a transitional probabilities approach. * $p < 0.01$, ** $p < 0.001$ vs control.

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Table VIII. Clinical efficacy of oral aprepitant (APR) in the prevention of chemotherapy-induced nausea and vomiting in patients (pts) with breast cancer[30] or various malignancies[31] receiving moderately emetogenic chemotherapy. Data were obtained from the modified intent-to-treat population[a] of randomized, double-blind, multicentre,[30,31] phase III trials. Data have also been obtained from the US prescribing information[6] and the EU summary of product characteristics.[13] Pts were randomised to an APR regimen (APR plus dexamethasone plus ondansetron) or a control (CON) regimen (dexamethasone plus ondansetron; see table VI for further details of dosage and days of administration). All antiemetic agents were administered orally. Placebo tablets/capsules were administered to maintain blinding. Efficacy endpoints were assessed in cycle 1 during the acute (day 1), delayed (days 2–5) or overall (days 1–5) phase after administration of chemotherapy

Study	Regimen (pt no.)	Phase	Endpoint[b] (% of pts)					
			complete response	complete protection	no emesis	no nausea	no significant nausea	no rescue medication
Rapoport et al.[31]	APR	Acute	89**		92**			
	(425)	Delayed	71**		78**			
		Overall	69**		76**[c]			
	CON	Acute	80		84			
	(407)	Delayed	61		67			
		Overall	56		62[c]			
Warr et al.[30]	APR	Acute	76*		88**		80	83
	(433)	Delayed	55		81**		65	63
		Overall	51*[c]	43	76**	33	61	59
	CON	Acute	69		77		78	80
	(424)	Delayed	49		69		62	60
		Overall	42[c]	37	59	33	56	56

a Pts who received chemotherapy and at least one dose of the study drug and had at least one post-treatment assessment during cycle 1.

b See table IV for definition of endpoints.

c Primary endpoint.

* $p<0.05$, ** $p<0.001$ vs CON (values not adjusted for multiplicity).

In the other study, patients with various malignancies were scheduled to be treated with a single dose of one or more of the following chemotherapeutic agents: any intravenous dose of oxaliplatin, carboplatin, epirubicin, idarubicin, ifosfamide, irinotecan, daunorubicin, or doxorubicin; intravenous cyclophosphamide $<1500\,mg/m^2$; or intravenous cytarabine $>1\,g/m^2$.[31] The various types of malignancies included breast (52% of patients), colorectal (20%), lung (13%) and ovarian cancer (4.6%).

Single-Cycle Chemotherapy

In patients with breast cancer treated with MEC, an aprepitant regimen, compared with a control regimen, was significantly more effective for the prevention of CINV, according to data from the large phase III trial.[30] Significantly ($p<0.05$) more patients treated with the aprepitant regimen had an overall complete response (primary endpoint) than with the control regimen alone (table VIII). Complete responses during the acute phase (table VIII) were also significantly higher with the aprepitant regimen than with the control regimen. When the separate components of complete response were analysed, significantly (unadjusted p-value <0.001) more recipients of the aprepitant than the control regimen reported no emesis during the overall, acute and delayed phases, but there was no significant difference between the groups for the use of rescue medication for any phase (table VIII). There was no significant difference between the groups during the overall phase for the percentage of patients reporting no nausea or no significant nausea.

Assessment of the impact of vomiting and nausea on the patients' daily lives (using the FLIE questionnaire) indicated that a higher proportion of patients treated with the aprepitant than the control regimen reported no or minimal impact on daily living overall (64% vs 56%; $p=0.019$), with significant differences favouring aprepitant in the vomiting domain score (86% vs

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72%; p < 0.001), but not the nausea domain score (54% vs 51%).[30]

Significantly (p < 0.001) more recipients of an aprepitant than a control regimen had no emesis (primary endpoint) and a complete response during the overall phase, according to preliminary data from a large phase III trial in patients with a variety of malignancies receiving MEC (table VIII). Significantly more recipients of the aprepitant regimen than the control regimen had no emesis and a complete response during the acute and delayed phases (table VIII).[31]

In a smaller, single-centre trial in Chinese patients with breast cancer treated with MEC, there was no significant difference between the treatment groups for the number of patients who reported complete responses, complete protection, no vomiting, no significant nausea, no nausea or no rescue medication during the overall, acute or delayed phases.[32] However, the impact of vomiting and nausea on the patients' daily lives (assessed according to the FLIE questionnaire) for the vomiting domain was significantly less for those treated with aprepitant than those treated with the control regimen (mean score 3.40 vs 23.99; p = 0.0002), although there was no significant between-group difference for the total score or for the nausea domain.[32]

Multiple-Cycle Chemotherapy

In a multiple-cycle extension[40] of the large phase III trial in patients with breast cancer,[30] the advantage of the antiemetic effect of the aprepitant regimen over the control regimen seen in cycle 1 (complete response 51% vs 43%; p = 0.015) was maintained throughout the additional three cycles of MEC (figure 2).

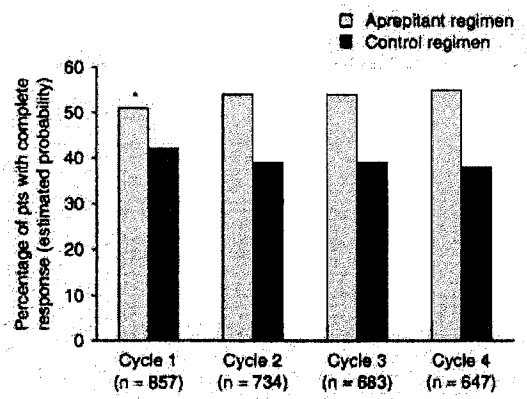


Fig. 2. Estimated probability of complete response in an individual cycle in the 5 days after treatment with moderately emetogenic chemotherapy (MEC) in breast cancer patients (pts).[40] Pts (n = 744) who had completed one cycle of chemotherapy in a randomized, double-blind, multicentre study (866 pts initially randomized) entered the multiple-cycle, extension study during which they received an additional three cycles of MEC and an aprepitant (aprepitant plus dexamethasone plus ondansetron) or control regimen (dexamethasone plus ondansetron; see table VI for details of dosage and days of administration) to prevent nausea and emesis. Analyses are based on the modified intent-to-treat population and used a transitional probabilities approach. * p = 0.015; statistical analyses not reported for cycles 2–4.

4.1.3 Special Populations

A randomized, double-blind, multicentre trial compared the efficacy of an aprepitant regimen (aprepitant plus dexamethasone plus ondansetron) with a control regimen (dexamethasone plus ondansetron) in the prevention of CINV in adolescent patients (n = 46) scheduled for treatment with emetogenic chemotherapy or a previously intolerable chemotherapy due to CINV.[16] Four patients also received open-label treatment with the aprepitant regimen.

Specific details of each regimen and the dosage of each of the antiemetic agents involved are presented in table IX. Patients were aged 11–19 years with confirmed malignancy and a Karnofsky score ≥60. Most patients had bone sarcoma (53% treated with the aprepitant regimen and 83% treated with the control regimen).[16]

Rates of complete response in the overall, acute and delayed phase were 29%, 61% and 36% in recipients of the aprepitant regimen and 6%, 39% and 6% with the control regimen, with no statistically significant difference between the two treatment groups.[16] Rates of no emesis and no use of rescue medication (during the acute, delayed and overall phase), and overall rates of no nausea were not significantly different between the two treatment groups. However, the study was not sufficiently powered to demonstrate a between-group difference in efficacy and the lack of statistical significance may have been due to the small sample size.

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Table IX. Aprepitant (APR) or control (CON) regimens used in a randomized, double-blind multicentre trial in adolescent patients aged 11–19 years treated with emetogenic chemotherapy. APR and DEX were administered orally and OND was administered intravenously

Regimen	Dose [day(s) administered]
APR	APR 125 mg [1][a] then 80 mg od [2, 3]
	DEX 8 mg [1][b] then 4 mg od [2–4]
	OND 0.45 mg/kg [1]
CON	DEX 16 mg [1][b] then 8 mg od [2–4]
	OND 0.45 mg/kg [1]

a Administered 1 h prior to chemotherapy.

b Administered 30 minutes prior to chemotherapy.

DEX = dexamethasone; **od** = once daily; **OND** = ondansetron.

4.2 Postoperative Nausea and Vomiting (PONV)

The efficacy of aprepitant was compared with that of ondansetron for the prevention of PONV in randomized, double-blind, multicentre, phase III trials in patients undergoing open, abdominal surgery under general anaesthesia.[41,42] This section focuses on data pertaining to the approved 40 mg dose of aprepitant.

Patients (n = 922[41] and 805[42]) were randomized to receive a single dose of oral aprepitant 40 or 125 mg (administered with 50 mL of water 1–3 hours before anaesthesia), or an intravenous dose of ondansetron 4 mg (administered immediately before induction of anaesthesia). Patients could not receive additional prophylactic antiemetics within 24 hours pre-operatively, intra-operatively or postoperatively, although patients could receive rescue antiemetics for established PONV.

Patients were aged ≥18 years with an American Society of Anesthesiologists physical status class of I–III and were scheduled to undergo open abdominal surgery requiring an overnight stay in hospital and to receive volatile agent-based anaesthesia including nitrous oxide. Patients who had vomited within the previous 24 hours or due to an organic aetiology were excluded from the trials.[41,42]

Of the 564 patients who received aprepitant 40 mg in both these trials,[41,42] 92% were women (who were mainly undergoing gynaecological surgery), 58% were White, 13% Hispanic American, 7% multi-racial, 14% Black, 6% Asian and 2% were from other races.[6] The mean age of patients treated with aprepitant 40 mg was 46.1 years (range 19–84 years).[6]

A primary efficacy endpoint in both trials was the complete response rate (see table IV for definition) in the 24 hours after surgery in the mITT population (866[41] and 733[42] patients). A co-primary endpoint in one of the trials was the rate of no vomiting in the 24 hours after surgery.[41] One trial assessed the noninferiority of aprepitant compared with ondansetron;[41] noninferiority was achieved if the lower bound for the one-sided 95% CI for the odds ratio of aprepitant versus ondansetron was >0.65.

One of the studies failed to met the primary hypothesis that aprepitant was superior to ondansetron, as measured by the proportion of patients with complete response.[42] However, the second study established that a single dose of aprepitant 40 mg was noninferior to ondansetron in achieving complete response (odds ratio 1.4; lower bound of the one-sided 95% CI was 1.04).[41]

Aprepitant 40 mg was significantly more effective than ondansetron at preventing vomiting at 24 and 48 hours after surgery in both studies ($p < 0.001$; table X).[41,42] Moreover, during the first 48 hours after surgery, aprepitant 40 mg, compared with ondansetron, delayed the time to the first vomiting episode ($p < 0.001$) in both studies. More aprepitant 40 mg than ondansetron recipients had no significant nausea ($p < 0.05$; table X) in one of the studies.[41] There was no significant between-group difference in the number of patients who did not require rescue medication (table X) in either of the studies.

According to *post hoc* analyses of pooled data from both of these trials, aprepitant 40 mg was significantly more effective than ondansetron for each of the five endpoints (figure 3) in the 24 hours after surgery, including: no significant nausea; no nausea; no vomiting; no nausea and no vomiting; and no nausea, no vomiting and no use of rescue medication.[43]

5. Pharmacoeconomic Considerations

A number of analyses have examined the cost effectiveness of an aprepitant regimen relative to

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Table X. Clinical efficacy of oral aprepitant (APR) compared with that of ondansetron (OND) in the prevention of postoperative nausea and vomiting in surgical patients (pts) in two, randomized, double-blind, multicentre, phase III trials.[41,42] Pts received a single oral dose of APR 40 or 125 mg (administered with 50 mL of water 1–3 hours before anaesthesia), or an intravenous dose of OND 4 mg (administered immediately before induction of anaesthesia)

Study	Dose (mg)	No. of pts (mITT)	Complete response[a] (% of pts) 0–24 h[b]	No vomiting (% of pts)		No rescue medication (% of pts) 0–24 h	No significant nausea[c] (% of pts) 0–24 h
				0–24 h	0–48 h		
Diemunsch et al.[41]	APR 40	293	84[d]	84**	82**	67	62*
	APR 125	293	83	86**	85**	65	60
	OND 4	280	55	71	66	63	53
Gan et al.[42]	APR 40	248	45	90**	85**[e]	45	50
	APR 125	239	43	95**	90**[f]	44	49
	OND 4	246	42	74	67[e]	46	43

a Defined as no vomiting and no use of rescue medication.

b Primary endpoint.

c Peak verbal rating scores of 0–4 on an 11-point scale; 0 (no nausea) to 10 (nausea as bad as could be).

d Noninferior to OND (lower bound of one-sided 95% CI >0.65).

e Data obtained from the US prescribing information.[6]

f Estimated from a graph.

mITT = modified intent-to-treat population; * $p<0.05$, ** $p<0.001$ vs OND.

a control regimen for the prevention of CINV in patients treated with HEC or MEC from a healthcare payer perspective.[44-46] Dosages of the agents involved in the regimens from the studies involved are presented in table V (HEC) and table VI (MEC). Further details of the methodology of the pharmacoeconomic studies are shown in table XI.

An aprepitant regimen compared with a control regimen was considered to be cost effective with regard to the cost per quality-adjusted life-year (QALY) in the prevention of CINV in two European studies,[44,45] although not according to a US analysis.[46] In the Belgian study,[45] an aprepitant regimen was predicted to dominate a control regimen for both MEC and HEC (i.e. were less expensive and more effective) based on incremental costs per QALY gained in both the trial-based and real-life approach that were tested in the model (year of costing 2005). The aprepitant regimen was estimated to be cost effective relative to the control regimen in the prevention of CINV during HEC in the German study, if a threshold value of €43 600 per QALY gained was used (year of costing 2004).[44] However, in the US analysis,[46] the incremental cost per QALY gained for the aprepitant regimen relative to the control regimen administered over five cycles of HEC exceeded the commonly accepted cost-effectiveness threshold of $US50 000 per QALY (year of costing 2005).

In the European studies, analyses demonstrated that the results were most sensitive to changes in the costs of hospitalization, rescue medication (German study[44]) and the cost of ondansetron (Belgian study). In the US study, sensitivity analyses indicated that the aprepitant regimen may be cost effective relative to the control regimen when rescue medication is costly or where the risk of delayed CINV is high.[46]

Pharmacoeconomic analyses, including those of aprepitant regimens, are subject to a number of limitations. Pharmacoeconomic analyses based on clinical trials extrapolate the results of such trials to the general population; however, patient populations, rates of compliance and major outcomes in clinical trials may differ from those observed in real-life practice. Modelled analyses, such as those presented in this section, rely on a number of assumptions and use data from a variety of sources. Results of pharmacoeconomic analyses may not be applicable to other

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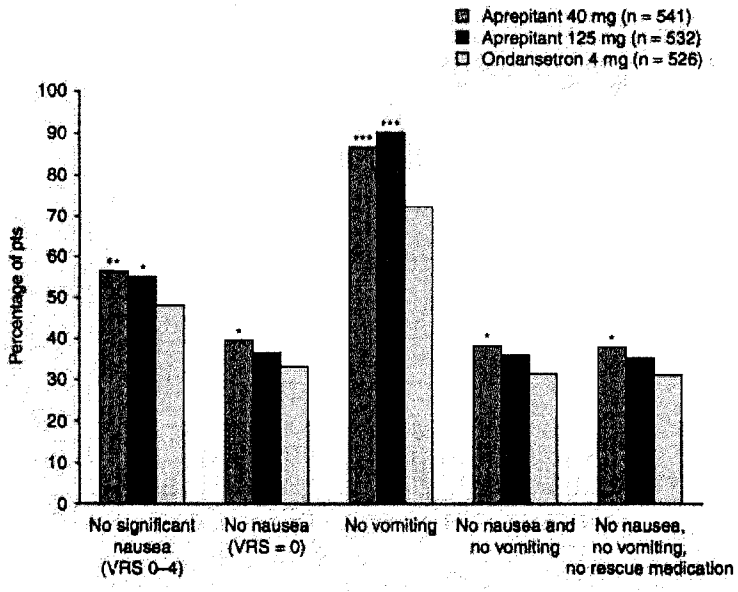


Fig. 3. *Post hoc* analysis of efficacy of aprepitant compared with ondansetron in the prevention of nausea and vomiting in the 24 hours after patients (pts) had undergone open abdominal surgery.[43] Combined analysis of data from the modified intent-to-treat population (n = 1559) from two randomized, double-blind trials.[41,42] Pts were randomized to receive a single dose of oral aprepitant 40 or 125 mg (administered with 50 mL of water 1–3 hours before anaesthesia), or an intravenous dose of ondansetron 4 mg (administered immediately before induction of anaesthesia). **VRS** = verbal rating score; an 11-point scale ranging from no nausea (0) to nausea as bad as it could be (10); * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs ondansetron.

geographical regions because of differences in healthcare systems, medical practice and unit costs.

6. Tolerability

6.1 CINV

The tolerability of an antiemetic regimen containing oral aprepitant (125 mg on day 1 then 80 mg once daily on days 2 and 3) has been investigated in patients receiving single or multiple cycles of HEC or MEC who participated in the clinical trials discussed in section 4. Aprepitant was administered in combination with ondansetron and dexamethasone (see table V and table VI for further details). Pooled analyses of the trials[6,13,35] (including those reported in the manufacturer's US prescribing information[6] and the EU summary of product characteristics[13]) are also discussed in this section.

6.1.1 Highly Emetogenic Chemotherapy

An aprepitant regimen was generally well tolerated in patients receiving a single cycle of HEC (cisplatin based), with most adverse events being mild to moderate in intensity.[6,27-29] The incidence of adverse events in recipients of an aprepitant regimen was similar to that in recipients of the control regimen (dexamethasone plus ondansetron).

According to a combined analysis[6,35] of two well controlled trials[27,28] in patients receiving one cycle of HEC, drug-related clinical adverse events were reported in ≈17% of the 544 recipients of the aprepitant regimen and ≈13% of the 550 recipients of the control regimen. Treatment was discontinued due to a clinical adverse event in 8% of patients treated with the aprepitant regimen and 6% of patients treated with the control regimen.[35] The adverse events that were reported in ≥10% of recipients of aprepitant were asthenia/fatigue, nausea, hiccups, constipation, diarrhoea and anorexia (see figure 4).

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Serious adverse events were reported in 13% and 14% of recipients of the aprepitant or control regimen.[35] Serious adverse events (regardless of causality) that were reported in the two studies included bradycardia, disorientation and perforated duodenal ulcer.[6]

Laboratory adverse events that occurred in ≥3% of recipients of the aprepitant or control regimen included increases in ALT (6% vs 4.3%), increases in AST (3.0% vs 1.3%), increases in blood urea nitrogen (4.7% vs 3.5%), increases in serum creatinine (3.7% vs 4.3%) and proteinuria (6.8% vs 5.3%).[6] The adverse experiences associated with the increases in ALT or AST were generally mild or moderate in intensity.

The tolerability profiles of an aprepitant regimen and a control regimen during the multiple-cycle extension (up to five additional cycles of chemotherapy) were generally similar to those observed after one cycle of HEC.[13] Drug-related clinical adverse events occurred in 6% and 4% of recipients of the aprepitant (n=413) or control (n=438) regimens during cycles 2–6.[36]

6.1.2 Moderately Emetogenic Chemotherapy

An aprepitant regimen was generally well tolerated in a studies in 866 evaluable patients with breast cancer[30] or 848 evaluable patients with various malignancies[31] receiving a single cycle of MEC.

The adverse event profile of an aprepitant regimen in patients receiving MEC was generally similar to that reported in patients receiving HEC. In recipients of an aprepitant regimen or a control regimen, the incidence of drug-related adverse events was 21.5% and 19.6% in the study

Table XI. Cost effectiveness of an aprepitant (APR) regimen (APR plus dexamethasone plus ondansetron) compared with a control (CON) regimen (dexamethasone plus ondansetron) in the prevention of chemotherapy-induced nausea and vomiting. Dosages of the agents involved in these regimens are presented in table V (highly emetogenic chemotherapy [HEC]) and table VI (moderately emetogenic chemotherapy [MEC]). All analyses are from a healthcare payer perspective

	Lordick et al.[44]	Annemans et al.[45]	Moore et al.[46]
Methodology			
Chemotherapy type	HEC	HEC; MEC	HEC
Source of efficacy data	Clinical trials[27,28,38]	HEC[29] and MEC[40] clinical trials (trial-based); longitudinal hospital database (real-life based)	Clinical trial[27]
Time horizon	5 days after a single cycle of chemotherapy	Four cycles (21 days) of chemotherapy	Five cycles (28-day) of chemotherapy
Discounting	Undiscounted	NR	NR
Study design	Decision analytical	Decision analytical	Markov
Year of costing	2004	2005	2005
Country of study	Germany	Belgium	US
Costs	Physician and hospitalization; antiemetic prophylaxis; rescue medication; unit costs for Germany were applied	Physician and hospitalization; antiemetic prophylaxis; rescue medication; unit costs for Germany were used and then adapted for Belgium	Clinic visit; laboratory costs antiemetic prophylaxis; rescue medication; unit costs for US were used
Incremental results (APR vs CON)			
QALYs gained HEC	0.0017	0.003 (trial-based and real-life based)	0.007
QALYs gained MEC		0.014 (trial-based and real-life based)	
Costs HEC	€49.60	−€66.84 (trial-based) and −€74.82 (real-life based)	$US682
Costs MEC		−€17.95 (trial-based) and −€21.70 (real-life based)	
Cost per QALY gained	€28 891	APR is dominant to CON for HEC and MEC (trial-based and real-life based)	$US97 429

NR = not reported; QALY = quality-adjusted life-year.

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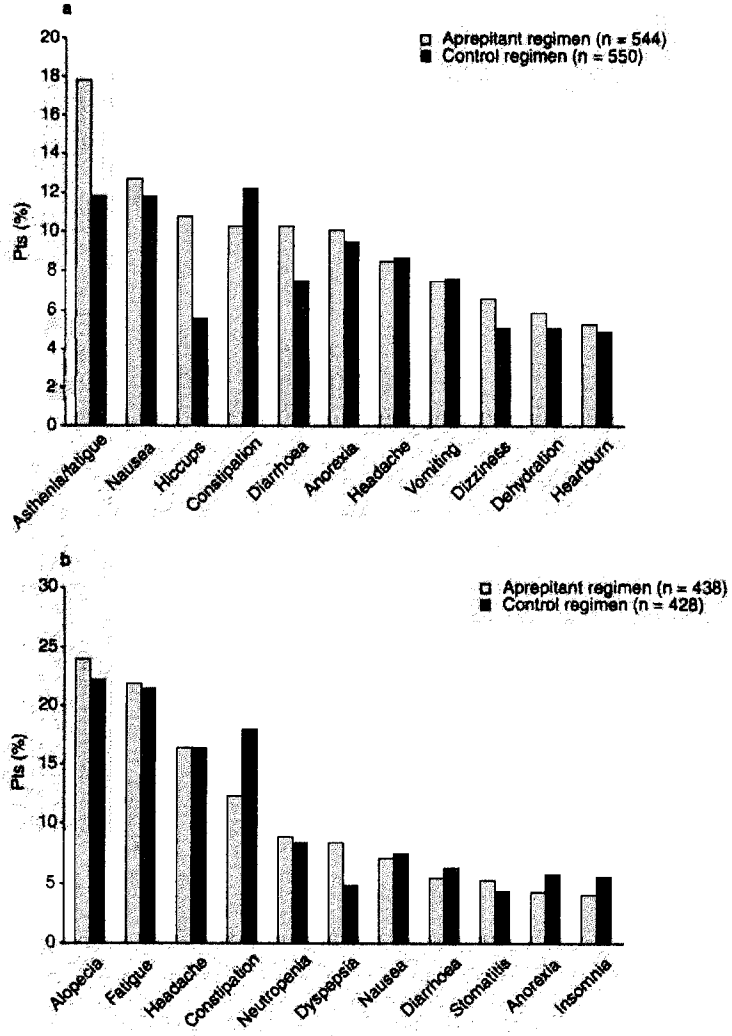


Fig. 4. Tolerability of an aprepitant regimen in patients (pts) treated with one cycle of emetogenic chemotherapy. Pts received a control regimen (ondansetron plus dexamethasone) or an aprepitant regimen (aprepitant plus ondansetron plus dexamethasone). Placebo tablets or capsules were administered to maintain blinding. Adverse events reported in ≥5% of either treatment regimen are shown. Nausea or vomiting were considered to be adverse events if they occurred after day 5 of the study or at any time if they were serious, drug related or resulted in discontinuation. Data were obtained from the manufacturer's US prescribing information.[6] Statistical analyses not reported. (a) A pooled analysis of two randomized, double-blind, multicentre trials in 1094 evaluable cancer pts treated with highly emetogenic (cisplatin-based) chemotherapy.[6] See table V for further details of dosage and days of administration of each antiemetic agent. (b) A randomized, double-blind, multicentre trial in 866 evaluable pts with breast cancer receiving moderately emetogenic chemotherapy.[6] See table VI for further details of dosage and days of administration of each antiemetic agent.

involving breast cancer patients,[30] and 7.2% and 9.3% in the study involving of the patients with various malignancies.[31] Most adverse events were mild to moderate in intensity. Less than 5% of patients reported serious adverse events, with the incidence being similar with the aprepitant or control regimen.[30] The incidences of discontinuations due to adverse events were 1.6%

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and 1.2% in the study involving patients with breast cancer,[30] and 0.2% and 0.5% in the study involving patients with various cancers.[31]

Adverse events that were reported in ≥5% of recipients of aprepitant included alopecia, fatigue, headache, constipation and dyspepsia,[30,31] with the incidence of these adverse events generally being similar to that in the control regimen (see figure 4 for the aprepitant tolerability profile in patients with breast cancer). In the trial in patients with breast cancer,[6] laboratory adverse events that occurred in ≥3% of recipients of the aprepitant or control regimen included decreases in haemoglobin (2.3% vs 4.7%) and decreases in white blood cell count (9.3% vs 9.0%).

The tolerability profiles of an aprepitant regimen and a control regimen during the multiple-cycle extension study[40] in patients with breast cancer (n = 744) administered up to five additional cycles of MEC were generally similar to those observed after one cycle of MEC.

6.2 PONV

The tolerability of a single oral dose of aprepitant 40 mg has been compared with that of a single intravenous dose of ondansetron in patients undergoing open, abdominal surgery who participated in two large, well controlled studies discussed in section 4.[41,42] Tolerability data have also been obtained from the pooled analyses of these trials reported in the aprepitant manufacturer's US prescribing information[6] and the EU summary of product characteristics.[13] In the combined analysis, 564 evaluable patients were administered aprepitant 40 mg and 538 evaluable patients were administered ondansetron 4 mg.

Drug-related clinical adverse experiences were reported in 6% of the aprepitant 40 mg recipients and 4% of the ondansetron recipients.[41,42] Most adverse events were mild to moderate in intensity. According to the combined analysis,[6] the tolerability profiles of aprepitant 40 mg and ondansetron 4 mg were similar, with the most commonly occurring adverse events (≥5% of patients) being constipation (8.5% vs 7.6%), nausea (8.5% vs 8.6%), pruritus (7.6% vs 8.4%), pyrexia (5.9% vs 10.6%), hypotension (5.7% vs 4.6%), headache (5.0% vs 6.5%) and flatulence (4.1% vs 5.8%). A laboratory adverse event that occurred in ≥3% of patients was a decrease in haemoglobin (3.8% vs 4.2%). Increases in ALT were reported in 1.1% of recipients of aprepitant 40 mg and 1.0% of recipients of ondansetron 4 mg.

7. Dosage and Administration

Aprepitant, in combination with other antiemetics, is indicated in various markets (including the US[6] and Europe[13]):

- for the prevention of nausea and vomiting associated with initial and repeat courses of MEC;
- for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of HEC (including high-dose cisplatin);
- for the prevention of PONV.

Aprepitant is not recommended for use in paediatric patients, as safety and efficacy have not been established in this population.[6,13] Aprepitant should not be given to pregnant patients unless its use is considered essential. Aprepitant is excreted in the milk of rats; however, it is not known if this agent is excreted in human milk. The US prescribing information notes that the decision as to whether to discontinue nursing or discontinue the aprepitant in nursing mothers should take into account the importance of the drug for the mother and the potential for serious adverse events in nursing infants and its potential for tumorigenicity in animal studies.[6] In Europe, breast feeding is not recommended during treatment with aprepitant.[13]

When used for the prevention of CINV, aprepitant should be administered for 3 days as part of a combination antiemetic regimen that includes a corticosteroid and a 5-HT_3 receptor antagonist. The recommended oral aprepitant dosage is 125 mg administered 1 hour prior to the initiation of chemotherapy (day 1) and 80 mg on the mornings of days 2 and 3.[6,13]

When used for the prevention of PONV, the recommended oral dose of aprepitant is 40 mg administered within 3 hours prior to anaesthesia.[6,13]

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Aprepitant should be used with caution when used concomitantly with drugs that are CYP3A4 substrates or inhibitors (see section 3.4).[6,13] Aprepitant should not be coadministered with pimozide, terfenadine, astemizole or cisapride. Concomitant corticosteroid dosages should be adjusted (see section 3.4). Weak inhibition of CYP3A4 by a single dose of aprepitant 40 mg is not expected to alter the plasma levels of concomitantly administered agents that are primarily metabolized through CYP3A4. The efficacy of aprepitant may be reduced when coadministered by drugs that are strongly induced by CYP3A4. Patients receiving oral contraceptives should use back-up or alternative contraception while they are receiving aprepitant (see section 3.4).

Administration of aprepitant to patients with severe hepatic insufficiency has not been studied; therefore, caution is advised when this agent is administered to this patient group. No dosage adjustment is required in patients with renal insufficiency.[6,13]

The local manufacturer's prescribing information should be consulted for detailed information regarding contraindications, warnings, drug interactions, patient monitoring recommendations and use in special patient populations.

8. The Place of Aprepitant in the Prevention of Nausea and Vomiting

Nausea and vomiting cause significant problems in patients recovering from surgical procedures carried out under general anaesthesia and in cancer patient receiving MEC or HEC. Benefits in terms of patients' recovery and health-related quality of life would be achieved with reductions in the incidence of CINV or PONV.[47]

To provide the greatest protection, antiemetic therapy should usually be administered prior to the administration of chemotherapy or prior to surgery. When used in the prevention of CINV, the antiemetic regimen should be continued for the duration of the effect of the chemotherapy involved.[4] Since no single agent can be expected to provide complete protection against the various phases of CINV, a combination of antiemetic agents is usually administered.

Before the advent of 5-HT_3 receptor antagonists, available antiemetics included phenothiazines, substituted benzamides, antihistamines, butyrophenones, corticosteroids, benzodiazepines and cannabinoids.[1,4] The introduction of 5-HT_3 receptor antagonists represented a major advance in the prevention of CINV and PONV.[1,4,48] These agents (see table XII) have been effective in controlling acute nausea and/or vomiting and are generally well tolerated, and their inclusion in a regimen aimed at preventing acute CINV is recommended (table XIII).[1] Although the first generation of 5-HT_3 receptor antagonists (including ondansetron, granisetron and dolasetron) are not generally effective in preventing delayed emesis, the second-generation 5-HT_3 receptor antagonist palonosetron has been effective in preventing acute CINV (during the first 24 hours following chemotherapy), and also exhibits prolonged efficacy to provide protection from CINV in the delayed and overall phases.[49,50] Oral forms of 5-HT_3 receptor antagonists are as effective as intravenous forms.

Corticosteroids (especially dexamethasone) are effective in the prevention of CINV.[4,51-53] The precise mechanism of action of corticosteroids in the prevention of emesis is uncertain but may involve a reduction of serotonin release or activation of corticosteroid receptors in the CNS.[54] Short-term corticosteroid therapy is generally well tolerated. Dexamethasone is effective in preventing acute and delayed nausea and vomiting and is included in most recommended preventive regimens (table XIII).

Table XII. Antiemetic agents

Class	Examples
Benzodiazepines	Lorazepam; olanzapine
Cannabinoids	Dronabinol; nabilone
Corticosteroids	Dexamethasone; methylprednisolone
Dopamine antagonists	Droperidol; haloperidol; metoclopramide; prochlorperazine; promethazine
Neurokinin-1 receptor antagonists	Aprepitant; fosaprepitant
Serotonin 5-HT_3 receptor antagonists	Dolasetron; granisetron; ondansetron; palonosetron; ramosetron and tropisetron

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Table XIII. Guideline recommendations for the prevention of chemotherapy-induced nausea and vomiting (CINV) and postoperative nausea and vomiting (PONV) in adult patients (pts). CINV guidelines for highly emetic chemotherapy (HEC) and moderately emetic chemotherapy (MEC) are presented from the American Society of Clinical Oncology (ASCO), the European Society for Medical Oncology (ESMO), the Multinational Association of Supportive Care in Cancer (MASCC) and National Comprehensive Cancer Network (NCCN). Consensus PONV guidelines from the Society for Ambulatory Anesthesia (SAMBA) are also presented

Guideline	Recommendation regimen[a]	
	Day 1	Day 2 onwards
CINV (HEC)		
ASCO[52]	APR + DEX + 5-HT_3 RA	APR + DEX
ESMO[60]	APR + COR + 5-HT_3 RA	APR + COR
MASCC[61]	APR[b] + DEX + 5-HT_3 RA	APR + DEX
NCCN[4]	APR[b] + DEX + 5-HT_3 RA[c]	APR + DEX ± LOR
CINV (MEC)		
ASCO[52]	APR[d] + DEX + 5-HT_3 RA	APR ± DEX[d]; or DEX
ESMO[60]	APR[d] + COR[e] + 5-HT_3 RA	APR + DEX[d]; or COR[f]; or 5-HT_3 RA[f]
MASCC[61]	APR[d] + DEX + 5-HT_3 RA	APR + DEX[d]; or DEX[f]; or 5-HT_3 RA[f]
NCCN[4]	APR[b,g] + DEX + 5-HT_3 RA[c]	APR ± DEX[h]; or DEX; or 5-HT_3 RA[c]
PONV		
SAMBA[62]	Combination of ≥1 (moderate risk) or ≥2 (high risk) antiemetic agents from different classes[i]	Another class of drugs[j]

a See guidelines for recommended dosage of each agent in pts receiving HEC or MEC.

b Intravenous fosaprepitant may be substituted for APR on day 1.

c LOR + histamine receptor antagonist or a proton pump inhibitor are recommended, but optional, additions.

d Pts treated with an anthracycline plus cyclophosphamide only.

e DEX is recommended in pts treated with APR.

f Pts treated with MEC other than anthracycline plus cyclophosphamide.

g In selected pts treated with MEC (e.g. carboplatin, cisplatin, doxorubicin, epirubicin, ifosfamide, irinotecan or methotrexate).

h In pts treated with APR on day 1.

i Recommended agents include 5-HT_3 RA, DEX or droperidol.

j Recommended agents include DEX, droperidol or promethazine, or a 5-HT_3 RA for pts who did not receive prophylaxis.

5-HT_3 RA = serotonin 5-HT_3 receptor antagonist; **APR** = aprepitant; **COR** = corticosteroid; **DEX** = dexamethasone; **LOR** = lorazepam.

NK_1 receptor antagonists provide a different and complementary mechanism of preventing emesis to other available antiemetics. NK_1 receptor antagonists act by blocking the binding of substance P at the NK_1 receptor in the brainstem emetic centre and the GI tract. Aprepitant is the first agent in this class to be approved (including the US,[6] Canada and Europe[13]) for use in the prevention of CINV or PONV (see section 7). Aprepitant is poorly soluble in aqueous solutions and therefore is administered orally. An intravenous form of the prodrug of aprepitant (fosaprepitant) has recently been approved by the US FDA and European Medicines Agency as a substitute for oral aprepitant on day 1 of a standard CINV prevention regimen.[13,55,56] Fosaprepitant is well tolerated, with a pharmacokinetic study demonstrating its bioequivalence to aprepitant.[57]

Other NK_1 receptor antagonists that are under investigation in the prevention of CINV and PONV include vofopitant, casopitant and rolapitant.[58,59]

Treatment guidelines for the prevention of CINV have been published by several organizations including the National Comprehensive Cancer Network (NCCN),[4] the American Society of Clinical Oncology,[52] the European Society for Medical Oncology[60] the Multinational Association of Supportive Care in Cancer[61] (table XIII). For cancer patients receiving HEC, the guidelines generally recommend the administration of 3 days of aprepitant (or a single

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intravenous dose of the prodrug fosaprepitant) in the antiemetic regimen; a corticosteroid (generally dexamethasone) plus any 5-HT_3 receptor antagonist are also recommended agents for inclusion. In cancer patients treated with MEC, current guidelines also recommend the administration of 3 days of aprepitant in selected patients. Some guidelines[52,60,61] restrict the use of this agent to patients to be treated with an anthracycline plus cyclophosphamide but the NCCN guidelines suggesting this agent should also be used in patients to be treated with other chemotherapies of moderate emetic risk (e.g. carboplatin, cisplatin, doxorubicin, epirubicin, ifosfamide, irinotecan, or methotrexate). If aprepitant (administered over 3 days) is used in patients treated with MEC, then generally the guidelines recommend its use in combination with dexamethasone and a 5-HT_3 receptor antagonist.

Comparison of prophylactic regimens in the prevention of CINV or PONV should take into account the effect of rescue medication on either nausea or vomiting. Once rescue medication has been administered, the lack of nausea and/or vomiting may be due to the prophylactic medication, the rescue medication or both. Thus, the trials that investigated the efficacy of aprepitant regimens generally used complete response (no emesis and no rescue medication) as the primary endpoint. Phase III trials have established (using this primary endpoint) that an aprepitant regimen was effective in the prevention of CINV and PONV.

Early studies involving aprepitant demonstrated that the triple combination of aprepitant with a corticosteroid and a 5-HT_3 receptor antagonist was more effective than the dual combination of a corticosteroid plus another agent in the prevention of cisplatin-induced emesis.[63,64] Subsequent large, phase III trials in patients with cancer (section 4.1.1) confirmed that aprepitant in combination with ondansetron and dexamethasone was more effective than a regimen of ondansetron and dexamethasone in achieving a complete response in the 5 days after administration of a single cycle of cisplatin-based HEC. Moreover, aprepitant was effective in the achievement of a complete response in both the acute and delayed phases. This preventative efficacy was maintained across multiple cycles of chemotherapy. The addition of aprepitant to a regimen containing ondansetron and dexamethasone significantly reduced the impact of CINV on the daily lives of the patients.

Similarly, aprepitant in combination with ondansetron and dexamethasone was more effective than ondansetron and dexamethasone in achieving a complete response and preventing emesis in the 5 days after administration of a single cycle of MEC in phase III studies involving patients with breast cancer or various malignancies. The advantage of the antiemetic effect of the aprepitant regimen over the control regimen seen after the first cycle of MEC was maintained throughout an additional three cycles in a multiple-cycle extension of the large phase III trial in patients with breast cancer (section 4.1.2).

The control of nausea in patients receiving MEC or HEC remains a significant problem.[2] The role of the 3-day aprepitant regimen in the prevention of nausea is unclear, with data from phase III studies being inconsistent. There was a significant difference between the aprepitant and control regimen in the number of patients with no nausea in the delayed and overall phases (table VII) in one[28] of the identical phase III studies in patients treated with HEC (section 4.1.1). In a phase III trial in breast patients receiving MEC,[30] there was no improvement in nausea when aprepitant was added to dexamethasone plus ondansetron (section 4.1.2). Given their differing mechanism of action, cannabinoids may be useful in chemotherapy-induced nausea;[2] however, trials that investigate the combination of a cannabinoid and aprepitant in the prevention of CINV have yet to be conducted.

Since palonosetron is the only 5-HT_3 receptor antagonist that is effective in preventing CINV during both the acute and delayed phases, phase I and II studies have investigated the efficacy of various regimens that combine this agent with aprepitant. An early phase II study found that a regimen of aprepitant (days 1–3) plus dexamethasone (days 1–3) plus palonosetron (day 1) was effective in patients (n = 58) receiving various

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moderately to moderate-highly emetogenic chemotherapies (complete response rate 78%).[65] The recent NCCN guidelines recommend the use of palonosetron as the preferred 5-HT_3 receptor antagonist (in combination with dexamethasone and aprepitant) in patients receiving HEC.[4] This recommendation was based on the results of a randomized study;[66] however, this study used a higher than recommended dosage of palonosetron and aprepitant was not included. In a pilot study in patients treated with HEC and aprepitant plus dexamethasone (days 1–4) plus palonosetron (day 1), a single dose of aprepitant 125 mg on day 1 displayed similar effectiveness to aprepitant administered as a 125 mg dose on day 1 followed by 80 mg on days 2–3.[67] Moreover, a single-day regimen consisting of oral aprepitant 285 mg plus oral dexamethasone plus intravenous palonosetron was effective (51% overall complete response) in 41 patients with breast cancer receiving MEC.[68] Phase III studies in patients receiving HEC or MEC that investigated the efficacy of a single-day regimen of this three-drug combination are warranted.

An aprepitant regimen compared with a control regimen was considered to be cost effective with regard to the cost per QALY in the prevention of CINV in two European studies, although not according to a US analysis (see section 5). In the European studies, the results were most sensitive to changes in the costs of hospitalization, rescue medication (German study) and the cost of ondansetron (Belgian study). In the US study, sensitivity analysis indicated that the aprepitant regimen may be cost effective relative to the control regimen when rescue medication is costly or where the risk of delayed CINV is high.

A single dose of oral aprepitant 40 mg was as effective as ondansetron in preventing PONV (assessed according to complete response in the 24 hours after surgery) in patients who had undergone general open abdominal surgery in two phase III studies (section 4.2). Aprepitant was significantly more effective than ondansetron at preventing vomiting in the 24 and 48 hours after surgery in both studies ($p < 0.001$). During the 48 hours after surgery, aprepitant compared with ondansetron, delayed the time to the first vomiting episode ($p < 0.001$) in both studies.

Aprepitant is generally well tolerated in patients when used in the prevention of CINV or PONV (section 6). In cancer patients receiving single or multiple cycles of HEC or MEC, the incidence of adverse events in recipients of an aprepitant regimen was similar to that in recipients of the control regimen. Commonly reported adverse events were asthenia/fatigue, nausea, hiccups, constipation, diarrhoea and anorexia. The incidence of adverse events with a single oral dose of aprepitant was similar to that with a single intravenous dose of ondansetron when these agents were used in the prevention of PONV. Commonly reported adverse events were similar to those when an aprepitant regimen was used in the prevention of CINV and included constipation, nausea, pruritus, pyrexia, hypotension, headache and flatulence.

Aprepitant is metabolised by CYP3A4. Moreover, aprepitant is also an inhibitor of CYP3A4 and an inducer of both CYP3A4 and CYP2C9. Consequently, aprepitant can cause a number of drug interactions (see section 3.4). The interactions tend to be more significant when the coadministered drug is administered orally rather than through the intravenous route due to first-pass metabolism. The manufacturer notes that caution should be exercised when aprepitant is coadministered with a number of agents including chemotherapeutic agents, with some drugs being contraindicated due to the interaction potential of aprepitant (see section 3.4 and section 7).

The prevention of nausea and vomiting involves a complex interaction between multiple organs and multiple neurotransmitters. Continued research is needed to provide the most effective antiemetic regimen. Such a regimen is likely to involve a combination of various antiemetic agents with different mechanisms of action. In this regard, research is warranted to clarify the role of aprepitant, when used alone or in combination with various other antiemetic agents, in various clinical situations including bone marrow transplantation, multiple-day chemotherapy regimens and radiotherapy-induced nausea.

In conclusion, when combined with a standard regimen of a corticosteroid (dexamethasone) and a serotonin 5-HT_3 receptor antagonist (ondan-

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setron), oral aprepitant (125 mg on day 1 then 80 mg once daily on days 2 and 3) was effective in the prevention of acute and delayed CINV associated with single or multiple cycles of HEC. This aprepitant regimen was also effective in the prevention of CINV in patients treated with single or multiple doses of MEC. A single oral dose of aprepitant 40 mg administered prior to patients undergoing abdominal surgery was also effective in the prevention of PONV. Aprepitant was generally well tolerated. Aprepitant is a recommended option for the treatment of PONV, and when combined with a corticosteroid and 5-HT_3 receptor antagonist is a recommended regimen for the treatment of CINV.

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References

1. Navari RM. Pharmacological management of chemotherapy-induced nausea and vomiting: focus on recent developments. Drugs 2009; 69 (5): 515-33
2. Navari RM. Antiemetic control: toward a new standard of care for emetogenic chemotherapy. Expert Opin Pharmacother 2009 Mar; 10 (4): 629-44
3. Gan TJ. Risk factors for postoperative nausea and vomiting. Anesth Analg 2006; 102 (6): 1884-9
4. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology™ Vol 3 [online]. Available from URL: http://www.nccn.org [Accessed 2009 Jun 30]
5. Dando TM, Perry CM. Aprepitant: a review of its use in the prevention of chemotherapy-induced nausea and vomiting. Drugs 2004; 64 (7): 777-94
6. Merck & Co., Inc. EMEND® (aprepitant) capsules: prescribing information. USA [online]. Available from URL: http://www.merck.com [Accessed 2009 Apr 10]
7. Huskey SE, Dean BJ, Bakhtiar R, et al. Brain penetration of aprepitant, a substance P receptor antagonist, in ferrets. Drug Metab Dispos 2003; 31 (6): 785-91
8. Bergström M, Hargreaves RJ, Burns HD, et al. Human positron emission tomography studies of brain neurokinin 1 receptor occupancy by aprepitant. Biol Psychiatry 2004 May 15; 55 (10): 1007-12
9. Hargreaves R. Imaging substance P receptors (NK1) in the living human brain using positron emission tomography. J Clin Psychiatry 2002; 63 Suppl. 11: 18-24
10. Hale JJ, Mills SG, MacCoss M, et al. Structural optimization affording 2-(R)-(1-(R)-3,5-bis(trifluoromethyl)phenylethoxy) -3-(S)-(4-fluoro)phenyl-4-(3-oxo-1,2,4-triazol-5-yl)methylmorpholine, a potent, orally active, long-acting morpholine acetal human NK-1 receptor antagonist. J Med Chem 1998 Nov 5; 41 (23): 4607-14
11. Tattersall FD, Rycroft W, Cumberbatch M, et al. The novel NK1 receptor antagonist MK-0869 (L-754,030) and its water soluble phosphoryl prodrug, L-758,298, inhibit acute and delayed cisplatin-induced emesis in ferrets. Neuropharmacology 2000 Feb 14; 39 (4): 652-63
12. Madsen JL, Fuglsang S. A randomized, placebo-controlled, crossover, double-blind trial of the NK1 receptor antagonist aprepitant on gastrointestinal motor function in healthy humans. Aliment Pharmacol Ther 2008 Apr 1; 27 (7): 609-15
13. European Medicines Agency. EMEND®: summary of product characteristics [online]. Available from URL: http://www.emea.europa.eu/humandocs/PDFs/EPAR/emend/H-527-PI-en.pdf [Accessed 2009 Apr 25]
14. Huskey SE, Dean BJ, Doss GA, et al. The metabolic disposition of aprepitant, a substance P receptor antagonist, in rats and dogs. Drug Metab Dispos 2003; 32 (2): 246-58
15. Sanchez RI, Wang RW, Newton DJ, et al. Cytochrome P450 3A4 is the major enzyme involved in the metabolism of the substance P receptor antagonist aprepitant. Drug Metab Dispos 2004 Nov; 32 (11): 1287-92
16. Gore L, Chawla S, Petrilli A, et al. Aprepitant in adolescent patients for prevention of chemotherapy-induced nausea and vomiting: a randomized, double-blind, placebo-controlled study of efficacy and tolerability. Pediatr Blood Cancer 2009 Feb; 52 (2): 242-7
17. Depré M, Van Hecken A, Oeyen M, et al. Effect of aprepitant on the pharmacokinetics and pharmacodynamics of warfarin. Eur J Clin Pharmacol 2005 Jul; 61 (5-6): 341-6
18. Bergman AJ, Marbury T, Fosbinder T, et al. Effect of impaired renal function and haemodialysis on the pharmacokinetics of aprepitant. Clin Pharmacokinet 2005; 44 (6): 637-47
19. McCrea JB, Majumdar AK, Goldberg MR, et al. Effects of the neurokinin1 receptor antagonist aprepitant on the pharmacokinetics of dexamethasone and methylprednisolone. Clin Pharmacol Ther 2003 Jul; 74 (1): 17-24
20. Blum RA, Majumdar A, McCrea J, et al. Effects of aprepitant on the pharmacokinetics of ondansetron and granisetron in healthy subjects. Clin Ther 2003 May; 25: 1407-19
21. Shah AK, Hunt TL, Gallagher SC, et al. Pharmacokinetics of palonosetron in combination with aprepitant in healthy volunteers. Curr Med Res Opin 2005 Apr; 21 (4): 595-601
22. Walko CM, Yu AY, Bhushan S, et al. Aprepitant's (AP) effect on cyclophosphamide (CPA) in early breast cancer patients: evaluation of pharmacokinetics [abstract no. 588]. J Clin Oncol 2009; 27 Suppl.: 15s
23. Nygren P, Hande K, Petty KJ, et al. Lack of effect of aprepitant on the pharmacokinetics of docetaxel in cancer patients. Cancer Chemother Pharmacol 2005 Jun; 55 (6): 609-16
24. Loos WJ, de Wit R, Freedman SJ, et al. Aprepitant when added to a standard antiemetic regimen consisting of ondansetron and dexamethasone does not affect vinorelbine pharmacokinetics in cancer patients. Cancer Chemother Pharmacol 2007 Feb; 59 (3): 407-12

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25. Feuring M, Lee Y, Orlowski LH, et al. Lack of effect of aprepitant on digoxin pharmacokinetics in healthy subjects. J Clin Pharmacol 2003 Aug; 43 (8): 912-7
26. Lindley CM, Hirsch JD, O'Neill CV, et al. Quality of life consequences of chemotherapy-induced emesis. Qual Life Res 1992 Oct; 1 (5): 331-40
27. Hesketh PJ, Grunberg SM, Gralla RJ, et al. The oral neurokinin-1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting: a multinational, randomised, double-blind, placebo-controlled trial in patients receiving high-dose cisplating: the aprepitant protocol 052 study group. J Clin Oncol 2003 Nov 15; 21 (22): 4112-9
28. Poli-Bigelli S, Rodrigues-Pereira J, Carides AD, et al. Addition of the neurokinin 1 receptor anatagonist aprepitant to standard antiemetic therapy improves control of chemotherapy-induced nausea and vomiting: results from a randomized, double-blind, placebo-controlled trial in Latin America. Cancer 2003 Jun 15; 97 (12): 3090-8
29. Schmoll HJ, Aapro MS, Poli-Bigelli S, et al. Comparison of an aprepitant regimen with a multiple-day ondansetron regimen, both with dexamethasone, for antiemetic efficacy in high-dose cisplatin treatment. Ann Oncol 2006 Jun; 17 (6): 1000-6
30. Warr DG, Hesketh PJ, Gralla RJ, et al. Efficacy and tolerability of aprepitant for the prevention of chemotherapy-induced nausea and vomiting in patients with breast cancer after moderately emetogenic chemotherapy. J Clin Oncol 2005 Apr 20; 23 (12): 2822-30
31. Rapoport BL, Jordan K, Boice JA, et al. Aprepitant for the prevention of chemotherapy-induced nausea and vomiting associated with a broad range of moderately emetogenic chemotherapies and tumor types: a randomized, double-blind study. Support Care Cancer. Epub 2009 Jul 1
32. Yeo W, Mo FK, Suen JJ, et al. A randomized study of aprepitant, ondansetron and dexamethasone for chemotherapy-induced nausea and vomiting in Chinese breast cancer patients receiving moderately emetogenic chemotherapy. Breast Cancer Res Treat 2009 Feb; 113 (3): 529-35
33. Chawla SP, Grunberg SM, Gralla RJ, et al. Establishing the dose of the oral NK1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting. Cancer 2003 May 1; 97 (9): 2290-300
34. de Wit R, Herrstedt J, Rapoport B, et al. Addition of the oral NK1 antagonist aprepitant to standard antiemetics provides protection against nausea and vomiting during multiple cycles of cisplatin-based chemotherapy. J Clin Oncol 2003 Nov 15; 21 (22): 4105-11
35. Warr DG, Grunberg SM, Gralla RJ, et al. The oral NK1 antagonist aprepitant for the prevention of acute and delayed chemotherapy-induced nausea and vomiting: pooled data from 2 randomised, double-blind, placebo controlled trials. Eur J Cancer 2005 Jun; 41 (9): 1278-85
36. de Wit R, Herrstedt J, Rapoport B, et al. The oral NK1 antagonist, aprepitant, given with standard antiemetics provides protection against nausea and vomiting over multiple cycles of cisplatin-based chemotherapy: a combined analysis of two randomised, placebo-controlled phase III clinical trials. Eur J Cancer 2004; 40: 403-10
37. Gralla RJ, de Wit R, Herrstedt J, et al. Antiemetic efficacy of the neurokinin-1 antagonist, aprepitant, plus a 5HT3 antagonist and a corticosteroid in patients receiving anthracyclines or cyclophosphamide in addition to high-dose cisplatin: analysis of combined data from two phase III randomized clinical trials. Cancer 2005 Aug 15; 104 (4): 864-8
38. Hesketh PJ, Grunberg SM, Herrstedt J, et al. Combined data from phase III trials of the NK1 antagonist aprepitant plus a 5HT3 antagonist and a corticosteroid for prevention of chemotherapy-induced nausea and vomiting: effect of gender on treatment response. Support Care Cancer 2006 Apr 1; 14 (4): 354-60
39. De Wit R, Hesketh PJ, Warr D, et al. The oral NK1 antagonist aprepitant for prevention of nausea and vomiting in patients receiving highly emetogenic chemotherapy. Am J Cancer 2005; 4 (1): 35-48
40. Herrstedt J, Muss HB, Warr DG, et al. Efficacy and tolerability of aprepitant for the prevention of chemotherapy-induced nausea and emesis over multiple cycles of moderately emetogenic chemotherapy. Cancer 2005 Oct 1; 104 (7): 1548-55
41. Diemunsch P, Gan TJ, Philip BK, et al. Single-dose aprepitant vs ondansetron for the prevention of postoperative nausea and vomiting: a randomized, double-blind phase III trial in patients undergoing open abdominal surgery. Br J Anaesth 2007 Aug; 99 (2): 202-11
42. Gan TJ, Apfel CC, Kovac A, et al. A randomized, double-blind comparison of the NK1 antagonist, aprepitant, versus ondansetron for the prevention of postoperative nausea and vomiting. Anesth Analg 2007 May; 104 (5): 1082-9
43. Diemunsch P, Apfel C, Gan TJ, et al. Preventing postoperative nausea and vomiting: post hoc analysis of pooled data from two randomized active-controlled trials of aprepitant. Curr Med Res Opin 2007 Oct; 23 (10): 2559-65
44. Lordick F, Ehlken B, Ihbe-Heffinger A, et al. Health outcomes and cost-effectiveness of aprepitant in outpatients receiving antiemetic prophylaxis for highly emetogenic chemotherapy in Germany. Eur J Cancer 2007 Jan; 43 (2): 299-307
45. Annemans L, Strens D, Lox E, et al. Cost-effectiveness analysis of aprepitant in the prevention of chemotherapy-induced nausea and vomiting in Belgium. Support Care Cancer 2008 Aug; 16 (8): 905-15
46. Moore S, Tumeh J, Wojtanowski S, et al. Cost-effectiveness of aprepitant for the prevention of chemotherapy-induced nausea and vomiting associated with highly emetogenic chemotherapy. Value Health 2007 Jan; 10 (1): 23-31
47. Bloechl-Daum B, Deuson RR, Mavros P, et al. Delayed nausea and vomiting continue to reduce patients' quality of life after highly and moderately emetogenic chemotherapy despite antiemetic treatment. J Clin Oncol 2006 Sep 20; 24 (27): 4472-8
48. Gan TJ. Selective serotonin 5-HT3 receptor antagonists for postoperative nausea and vomiting: are they all the same? CNS Drugs 2005; 19 (3): 225-38
49. Siddiqui MAA, Scott LJ. Palonosetron. Drugs 2004; 64 (10): 1125-32
50. Aapro MS. Palonosetron as an anti-emetic and anti-nausea agent in oncology. Ther Clin Risk Manag 2007 Dec; 3 (6): 1009-20
51. Stieler JM, Reichardt P, Riess H, et al. Treatment options for chemotherapy-induced nausea and vomiting: current and future. Am J Cancer 2003; 2 (1): 15-26

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52. Kris MG, Hesketh PJ, Somerfield MR, et al. American Society of Clinical Oncology guideline for antiemetics in oncology: update 2006. J Clin Oncol 2006 Jun 20; 24 (18): 2932-47
53. Ioannidis JP, Hesketh PJ, Lau J. Contribution of dexamethasone to control of chemotherapy-induced nausea and vomiting: a meta-analysis of randomized evidence. J Clin Oncol 2000 Oct 1; 18 (19): 3409-22
54. Grunberg SM. Antiemetic activity of corticosteroids in patients receiving cancer chemotherapy: dosing, efficacy, and tolerability analysis. Ann Oncol 2007 Feb; 18 (2): 233-40
55. Van Belle SJ, Cocquyt V. Fosaprepitant dimeglumine (MK-0517 or L-785,298), an intravenous neurokinin-1 antagonist for the prevention of chemotherapy induced nausea and vomiting. Expert Opin Pharmacother 2008 Dec; 9 (18): 3261-70
56. Merck & Co., Inc. Emend® (fosaprepitant dimeglumine) for injection [online]. Available from URL: http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/022023s001lbl.pdf [Accessed 2009 Jun 23]
57. Lasseter KC, Gambale J, Jin B, et al. Tolerability of fosaprepitant and bioequivalency to aprepitant in healthy subjects. J Clin Pharmacol 2007 Jul; 47 (7): 834-40
58. Diemunsch P, Joshi GP, Brichant JF. Neurokinin 1 receptor antagonists in the prevention of postoperative nausea and vomiting. Br J Anaesth 2009 May 19; 103 (1): 7-13
59. Navari RM. Casopitant, a neurokinin-1 receptor antagonist with anti-emetic and anti-nausea activities. Curr Opin Investig Drugs 2008 Jul; 9 (7): 774-85
60. Herrstedt J, Roila F. Chemotherapy-induced nausea and vomiting: ESMO clinical recommendations for prophylaxis. Ann Oncol 2008 May; 19 Suppl. 2: ii110-2
61. Multinational Association of Supportive Care in Cancer. Perugia International Cancer Conference VII: antiemetic guidelines [online]. Available from URL: http://data.memberclicks.com/site/masec/MASCC_Guidelines_Update.pdf [Accessed 2008 Jun 22]
62. Gan TJ, Meyer TA, Apfel CC, et al. Society for Ambulatory Anesthesia guidelines for the management of postoperative nausea and vomiting. Anesth Analg 2007 Dec; 105 (6): 1615-28, table of contents
63. Campos D, Pereira JR, Reinhardt RR, et al. Prevention of cisplatin-induced emesis by the oral neurokinin-1 antagonist, MK-869, in combination with granisetron and dexamethasone or with dexamethasone alone. J Clin Oncol 2001 Mar 15; 19 (6): 1759-67
64. Van Belle S, Lichinitser MR, Navari RM, et al. Prevention of cisplatin-induced acute and delayed emesis by the selective neurokinin-1 antagonists, L-758,298 and MK-869. Cancer 2002 Jun 1; 94 (11): 3032-41
65. Grote T, Hajdenberg J, Cartmell A, et al. Combination therapy for chemotherapy-induced nausea and vomiting in patients receiving moderately emetogenic chemotherapy: palonosetron, dexamethasone, and aprepitant. J Support Oncol 2006 Sep; 4 (8): 403-8
66. Saito M, Aogi K, Sekine I, et al. Palonosetron plus dexamethasone versus granisetron plus dexamethasone for prevention of nausea and vomiting during chemotherapy: a double-blind, double-dummy, randomised, comparative phase III trial. Lancet Oncol 2009 Feb; 10 (2): 115-24
67. Herrington JD, Jaskiewicz AD, Song J. Randomized, placebo-controlled, pilot study evaluating aprepitant single dose plus palonosetron and dexamethasone for the prevention of acute and delayed chemotherapy-induced nausea and vomiting. Cancer 2008 May 1; 112 (9): 2080-7
68. Grunberg SM, Dugan M, Muss H, et al. Effectiveness of a single-day three-drug regimen of dexamethasone, palonosetron, and aprepitant for the prevention of acute and delayed nausea and vomiting caused by moderately emetogenic chemotherapy. Support Care Cancer 2009 May; 17 (5): 589-94

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Development of aprepitant, the first neurokinin-1 receptor antagonist for the prevention of chemotherapy-induced nausea and vomiting

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Chemotherapy can be a life-prolonging treatment for many cancer patients, but it is often associated with profound nausea and vomiting that is so distressing that patients may delay or decline treatment to avoid these side effects. EMEND™ (aprepitant) is the first and only neurokinin-1 (NK-1) receptor antagonist available on the market for the prevention of acute and delayed chemotherapy-induced nausea and vomiting (CINV). Aprepitant acts centrally at NK-1 receptors in vomiting centers within the central nervous system to block their activation by substance P released as an unwanted consequence of chemotherapy. By controlling nausea and vomiting, EMEND helps improve patients' daily living and their ability to complete multiple cycles of chemotherapy. The development of aprepitant included a novel nanoparticle formulation to optimize oral absorption and innovative chemistry to discover a prodrug form suitable for intravenous administration to improve compliance and convenience for healthcare professionals and cancer patients.

Keywords: EMEND; aprepitant; neurokinin-1 receptor antagonist; chemotherapy-induced nausea and vomiting; cancer

Introduction

Cancer is one of the leading causes of death worldwide, and its incidence is increasing rapidly as the worldwide population continues to grow and age. Despite truly meaningful progress in the field of targeted chemotherapy, many cancer treatment regimens still use cytotoxic chemotherapeutic agents that produce profound emesis and nausea that occur acutely on the day of chemotherapy and then reappear some days later—often at home away from the gaze and care of the oncologist's office. These debilitating and feared side effects are well documented in open-access sites, such that informed patients who research their cancer treatment options often delay or postpone their therapy and sometimes completely refuse or withdraw from the very therapy that has been prescribed to prolong or save their lives. Control of chemotherapy-induced nausea and vomiting (CINV) is therefore a significant factor in ensuring that oncology patients maintain quality of life during their treatment regimens to get the full benefit of chemotherapy.

Drug therapies have been previously developed for the prevention of nausea and vomiting associated with anticancer chemotherapy (Fig. 1A). In the 1960s, phenothiazine dopamine D_2 receptor antagonists such as prochlorperazine (Compazine®, Stemetil®) that are potent antipsychotic compounds were used to control emesis, but these have several potential mechanistic side-effect liabilities including causing dyskinesias. In the 1980s, it was found that high doses of the dopamine D_2 receptor-5-HT_3 receptor antagonist metoclopramide combined with the steroid dexamethasone had improved efficacy particularly in the control of acute CINV 0–24 h postchemotherapy. In the 1980s, research showed that it was the 5-HT_3 receptor

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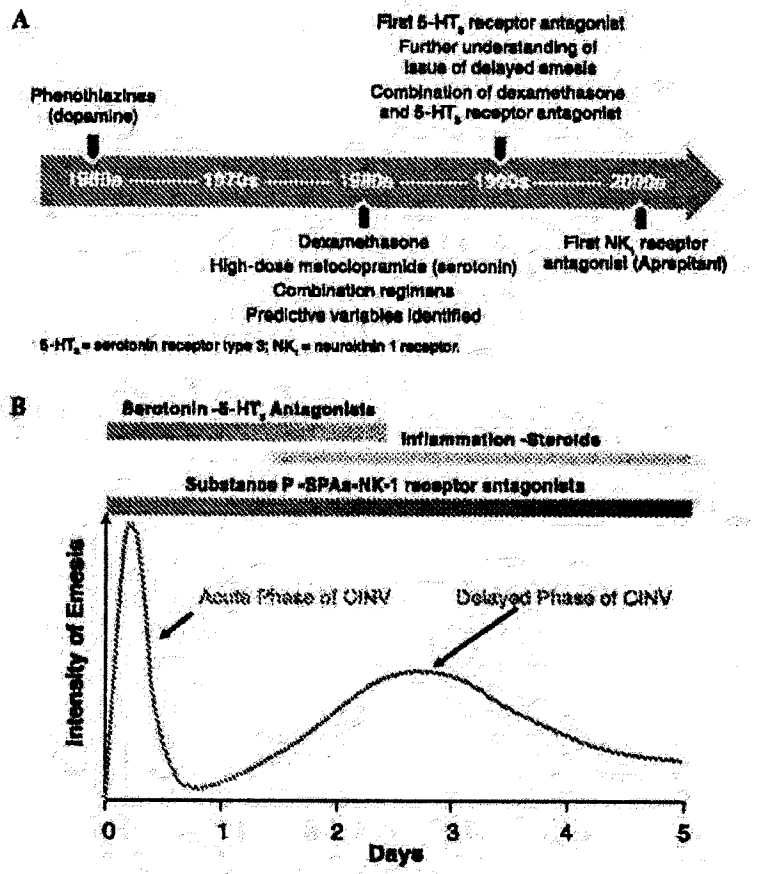


Figure 1. (A) Timeline of agents discovered to prevent emesis. (B) Time course of emesis and drug-sensitive phases.

component of metoclopramide that underpinned its efficacy in CINV, spurring the development of selective 5-HT_3 receptor antagonist drugs with improved tolerability by removing the liability of D_2 receptor antagonism. The first of these to be registered in the 1990s was ondansetron (ZOFRAN®), which was effective in the control of acute CINV with some additional benefit in the delayed phase of CINV (>24–120 h after chemotherapy) when combined with a corticosteroid such as dexamethasone. However, although combined therapy with these two agents provided control of CINV symptoms in the acute phase, their protective actions were poor during the delayed phase of CINV, which often occurs at home away from the oncology clinic some days later. Therefore, there remained an important unmet medical need for novel treatment agents to further improve control of CINV, especially in the delayed phase. Throughout the 1990s, research focused on the role of substance P and neurokinin-1 (NK-1) receptors in emesis and, in particular, the protective effects of NK-1 receptor antagonists against the acute and delayed emetic responses to chemotherapeutic agents (Fig. 1B). In 2003, EMEND® (aprepitant) became the first and is still the only NK-1 receptor antagonist available on the market for the prevention of CINV in cancer patients. EMEND provides a significant improvement in the number of patients who can tolerate their cancer chemotherapy without episodes of vomiting, particularly during the delayed phase, thereby

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improving their quality of life and allowing them to complete and benefit from the full course of their chemotherapeutic treatment regimens.

History of the development of aprepitant

The substance P story has been nearly 80 years in the telling—from the isolation of the peptide, to its sequencing, to the cloning of its receptor and the synthesis of the first small molecule antagonists. The journey began in 1931 when a pharmacologically active substance was isolated from the brain and intestine and named substance P—"P" for powder—by the pioneering pharmacologist John Gaddum working with Ulf von Euler.[1] In 1954, Gaddum continued his research into this extract and showed that substance P was concentrated in the emetic centers of the brain, commenting in his manuscript in the *Journal of Physiology* that "it is tempting to speculate why this is so."[2] It was not until 40 years later, in 1971, that the active substance, an 11-amino acid peptide, was isolated, sequenced, and synthesized *de novo* by Susan Lehman and her group.[3,4] Yet another 20 years went by, to 1991, before the receptor for substance P, the NK-1 receptor, was identified and cloned,[5] and small-molecule blockers or antagonists of substance P that could access these NK-1 receptors in the emetic centers in the brain were developed. Amazingly, in line with Gaddum's speculation, these substance P antagonists (SPAs) were shown to be the broadest spectrum antiemetics ever described.

Research at Merck began during the 1980s to discover SPAs with which to understand the role of substance P in health and disease. For many years this proved a difficult task, and only peptide antagonists that were unsuitable as oral drug candidates and that did not cross the blood–brain barrier were synthesized. In the early 1990s, the first small molecule brain-penetrant SPAs became available,[6] enabling the investigation of the therapeutic potential of the NK-1 antagonist mechanism. Despite strong anatomical evidence supporting a potential role for substance P in pain and affective disorders, the SPAs were inactive as analgesics and as antidepressants. The hypothesis that substance P was involved in emesis was initially supported by three preclinical observations: substance P was localized in the emetic centers of the brain, substance P could cause emesis, and depletion of substance P using a toxin (resiniferatoxin) could prevent emesis in preclinical species with a vomiting reflex. The critical proof that the substance P/NK-1 receptor axis played a crucial role in mediating the vomiting response to a number of stimuli came with demonstration that highly selective SPAs had profound activity against emesis induced by broad range of central and peripherally acting emetogens.[7,8] Moreover, these SPAs were active in multiple species with a vomiting reflex against a broad range of emetogens,[9] giving high confidence that the mechanism would translate to clinically meaningful activity.[10] In particular, SPAs were active against emesis induced by chemotherapeutic agents such as cisplatin and uniquely against the delayed phase of emesis that can recur days after treatment with such cytotoxic agents.[11] Continued research into the antiemetic mechanism of action of the SPAs showed that SPA molecules had to penetrate the brain to access central NK-1 receptors in the brain-stem emetic centers in order to be effective in preclinical models. Potent SPAs that did not cross into the brain were ineffective as antiemetics.[12] Aprepitant[13] was chosen for development on the basis of its notable efficacy and long duration of action in the preclinical emesis assays.

PET imaging NK-1 receptors in the brain

Confirmation that drugs reach their targets using markers of engagement is key to successful proof-of-concept testing, especially for drugs acting in the brain. Knowing how hard and how long a drug must hit its target to produce the desired pharmacologic effect is important for dose selection and clinical trial design and interpretation. During the aprepitant program, a novel PET tracer that imaged NK-1 receptors in living human brain was developed to visualize the central sites of action of aprepitant and to assess their occupancy by therapeutic doses of the drug (Fig. 2). Understanding the relationships between dose, plasma concentration, and receptor occupancy for aprepitant helped establish the link between target engagement and changes in the CINV clinical endpoint. This knowledge was important in the selection of the dosing regime for the regulatory filing of aprepitant and ensured that the lowest drug exposure that achieved target engagement consistent with >90% blockade of NK-1 receptors was chosen, thereby maximizing the potential therapeutic safety window of aprepitant.[14,15] The PET tracer was also used to predict the

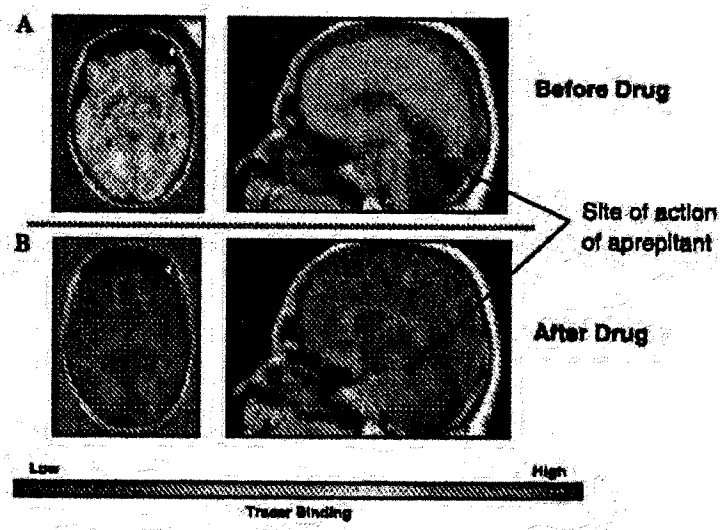


Figure 2. Occupancy of central NK-1 receptors by aprepitant visualized using PET imaging.

bioequivalence of different oral formulations of the drug by linking plasma concentration rather than dose to brain receptor occupancy and clinical efficacy. This was important information because the oral formulation of aprepitant required considerable optimization (see below).

Synthesis of aprepitant: a chemistry challenge

Synthesizing the aprepitant molecule is a synthetic chemistry challenge as it comprises two heterocyclic rings and three stereogenic centers in close proximity. A first-generation route was used for the production of 100 kg of aprepitant, but was deemed not sufficiently economical or environmentally benign for commercial manufacturing. The first-generation synthesis required several hazardous chemicals, such as sodium cyanide, dimethyltitanocene, and gaseous ammonia, and used extremely low temperatures in some steps. In addition, the route was poorly efficient, generating a large quantity of waste. As aprepitant moved through clinical trials and closer to regulatory filing, it became clear that a completely new route was required to address these liabilities. A team of process chemists went back to the drawing board, examined a number of alternate routes, and ultimately designed and developed a novel and efficient manufacturing route.

The streamlined synthesis used a "crystallization-induced asymmetric transformation."[16] In this process, the desired isomer of aprepitant crystallizes, and, simultaneously, the unwanted isomer is converted to the desired isomer, ultimately providing aprepitant in high yield and purity. This chemistry innovation halved the number of process steps while doubling the overall yield of aprepitant. The synthesis eliminated several hazardous chemicals; used 80% fewer raw materials, reagents, solvents, and less water; and was more energy efficient. The overall waste production was reduced by 85% as compared to the first-generation synthesis. This significant minimization of environmental impact was recognized by the U.S. Environmental Protection Agency in awarding their prestigious 2005 Presidential Green Chemistry Challenge Award to Merck & Co., Inc. for the redesign of the synthesis of aprepitant. Since the manufacturing process innovation occurred during the first year of aprepitant production, these benefits will be realized over the entire life cycle of EMEND.

Biopharmaceutical sciences: oral formulation of aprepitant

Early clinical tablet formulations of aprepitant showed highly variable, large food effects on absorption. Given the targeted patient population, development of a more bioavailable formulation was

crucial for the program. A number of alternate formulations such as liquid-filled capsules, alternative excipients, and amorphous drug substances were tested, but all met with limited success. Ultimately, a nanoparticle formulation that enhanced bioavailability and attenuated the food effect was developed using NanoCrystal® technology, licensed to Merck from Elan/Nanosystems. This process involved media milling of drug particles to <200 nanometers, coating onto beads, and encapsulation to provide a convenient formulation for the patient.[17] EMEND was approved by the U.S. Food and Drug Administration (FDA) in 2003. EMEND is dosed orally as a 125 mg tablet on the first day of chemotherapy treatment and as an 80 mg tablet on days two and three after chemotherapy.

Fosaprepitant: a prodrug of aprepitant for intravenous use

The sparing water solubility of aprepitant precluded its formulation in a vehicle acceptable for intravenous administration in humans. Since the availability of both an oral and an intravenous formulation of aprepitant would increase the delivery options available to oncologists and patients and provide maximum clinical dosing flexibility, we sought ways to overcome the solubility issues associated with aprepitant. An unprecedented prodrug strategy was undertaken in the chemistry program to discover a chemical form of aprepitant that had good water solubility, with the potential to be rapidly metabolically converted *in vivo* to the parent aprepitant while releasing innocuous residues, yet exhibited sufficient chemical stability to allow for routine handing and storage. The *N*-phosphoryl derivative of aprepitant (fosaprepitant) was synthesized,[18] and it was shown in a series of preclinical experiments to be metabolically converted to aprepitant both *in vitro* and *in vivo*, as well as to be functionally equivalent to aprepitant *in vivo*. Clinical studies then showed that fosaprepitant has a favorable tolerability in humans and excellent efficacy in the treatment of chemotherapy-induced emesis, thereby demonstrating the viability of the prodrug strategy for the intravenous delivery of aprepitant.[19] Fosaprepitant was approved in 2008. EMEND (fosaprepitant dimeglumine) for Injection (also known as IVEMEND® in Europe) 115 mg can be substituted for the 125 mg oral capsule of aprepitant on the first day of chemotherapy treatment.

Clinical development of aprepitant

During the clinical phase of development, aprepitant was studied in more than 6,500 patients in randomized controlled trials, and showed statistically significant and clinically meaningful reductions in the incidence of CINV associated with moderately to highly emetogenic chemotherapy compared with the prior standard regimen of a 5-HT_3 receptor antagonist and dexamethasone, and was well tolerated.[20–26]

Aprepitant for control of postoperative nausea and vomiting

The control of postoperative nausea and vomiting (PONV) has recently been reviewed.[27] Similar to CINV, PONV has a delayed phase response known as postdischarge nausea and vomiting (PDNV). PONV and PDNV impact recovery after anesthesia immediately after surgery and at later times (24–72 h) after surgical interventions when day-care patients are sent home, at which time there is no simple access to rescue medications or medical care. Given the broad preclinical spectrum of antiemetic control observed preclinically with the SPAs and their unique clinical efficacy in the delayed phase of CINV, clinical studies were undertaken to compare their efficacy to 5-HT_3 receptor antagonists, the previous standard of care.[28] These studies demonstrated the efficacy of aprepitant as monotherapy for the prevention of postoperative nausea and vomiting, and it was approved for this indication in 2006.

Aprepitant: learning about the biology of chemotherapy-induced emesis

The development of aprepitant provided new insights into the pharmacological and pathophysiological mechanisms involved in emesis. Both peripheral (glosophararyngeal and vagal nerves) and central (cortical and cerebellar) pathways can activate neuronal nuclei in the brainstem and trigger a sequence of events that results in the vomiting reflex (Fig. 3A). The 5-HT_3 receptor antagonists are thought to exert their actions predominantly on the peripheral terminals of vagal afferents in the gastrointestinal tract and in the chemoreceptor trigger zone (CRTZ) that lays in the area postrema outside of the blood–brain barrier to block the activating effects of serotonin released during chemotherapy. The CRTZ signals to another area, the nucleus

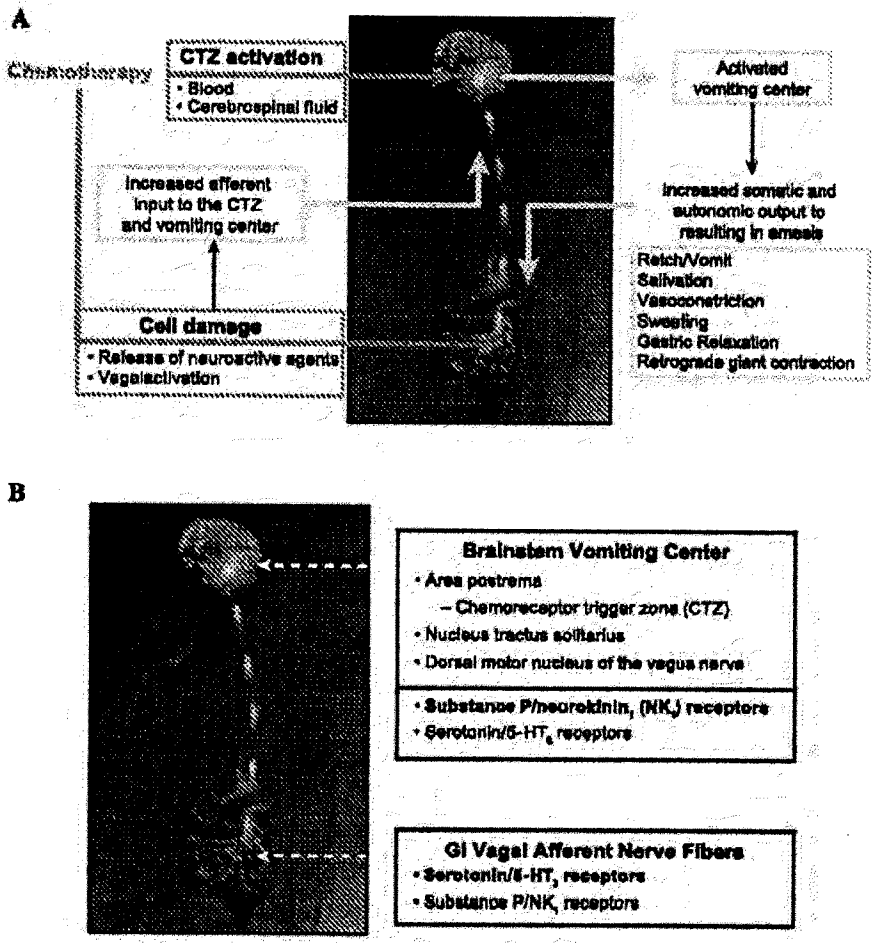


Figure 3. (A) Mechanism of chemotherapy-induced emesis. (B) Sites of action of 5-HT_3 and NK-1 receptor antagonists. Graphics by Kirk Moldoff.

tractus solitarius (NTS), in the brain stem that also receives emetogenic stimuli from higher brain centers (e.g., cortical and vestibular) as well as gastrointestinal vagal afferents, and is thought to orchestrate the patterns of central activity underlying CINV and PONV. Preclinical studies suggest that it is here within the NTS that SPAs such as aprepitant exert their strongest antiemetic properties through central inhibition of the emesis pattern generator (Fig. 3B). This central site of action is the likely explanation for the unique broad antiemetic pharmacological profile of the SPAs, indicating that substance P acting at central NK-1 receptors is one of the final common mechanisms involved in activation and coordination of the vomiting reflex.[29]

The acute and delayed clinical time course of CINV has previously been linked to serotonin release and inflammation by the clinical effectiveness of 5-HT_3 antagonists and steroids, respectively. The discovery of the SPAs and clinical experience with aprepitant has furthered our understanding and provided substantial evidence for involvement of substance P throughout the CINV response. The prolonged efficacy profile of aprepitant, including the delayed phase, indicates that substance P acting at central NK-1 receptors becomes increasingly important with time in the pathophysiology of the overall CINV response.[30] These observations support the clinical rationale for combination therapy with 5-HT_3 receptor antagonists (e.g.,

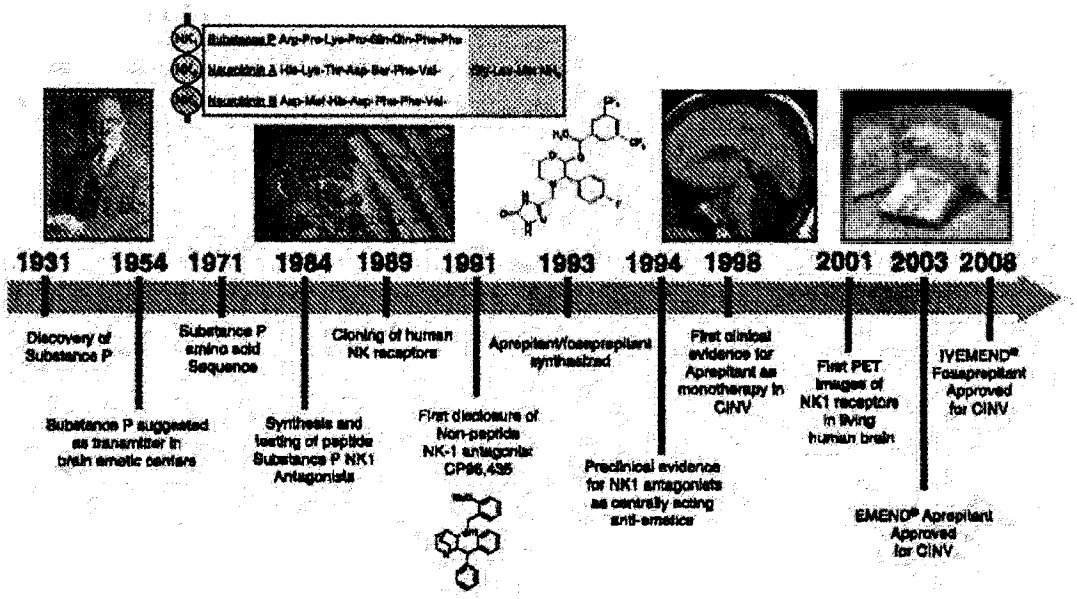


Figure 4. Substance P: 70 years from discovery to therapeutic utility. The photograph of Gaddum is reprinted by permission from Macmillan Publishers Ltd: *Nature* 406, 831 (24 August 2000), copyright 2000.

ondansetron), steroids (e.g., dexamethasone), and SPAs such as aprepitant to optimize control of CINV.

Current and future challenges in the aprepitant program

Ongoing discovery and development efforts in the program aim to identify simplified dose regimens of aprepitant. In August 2010, a single-dose formulation of fosaprepitant for IV administration was approved in the European Union for use instead of the 3-day oral regimen of aprepitant, together with a 5-HT_3 receptor antagonist and a corticosteroid. Additionally, in November 2010, the FDA approved a single-dose formulation, EMEND for Injection 150 mg, for patients receiving highly emetic chemotherapy. This new regimen provides a more simple treatment to patients who will not need to worry about taking capsules of EMEND on days two and three, ensuring compliance with therapy and improving convenience for both patients and healthcare professionals.

The incidence of cancer in pediatric patients is still a concern despite the availability of treatments for the different tumors and the resilience of the patients. There are no clear guidelines for antiemetic therapy in pediatric cancer patients since the available scientific data are very limited; this allows pediatric cancer patients to go through their chemotherapy treatment with suboptimal therapy for prevention of CINV. An age-appropriate formulation of aprepitant (powder for suspension) is currently under research and development to extend its benefits to pediatric patients.

Conclusion

Aprepitant today represents the culmination of more than 80 years of research into the pharmacology and physiology of substance P and more than 20 years of drug discovery and development toward identifying a safe, potent, orally active, and brain-penetrant SPA[31] (Fig. 4). Its discovery and development has dramatically improved the quality of life for patients with cancer who must undergo multiple cycles of chemotherapy. Aprepitant is the first and only substance P/NK-1 receptor antagonist available for the prevention of CINV in cancer patients. Aprepitant, in combination with a 5-HT_3 receptor antagonist and dexamethasone, optimizes protection against CINV in both the acute and delayed phases compared to the prior standard of care, and is now recommended as first-line therapy for patients about to be treated with moderately or highly emetogenic chemotherapy.

Conflicts of Interest

The authors are employees of Merck Sharp & Dohme Corp.

References

1. von Euler, U.S. & J.H. Gaddum. 1931. An unidentified depressor substance in certain tissue extracts. *J. Physiol. (Lond.)* 72: 74–87.
2. Amin, A.H., T.B.B. Crawford & J.H. Gaddum. 1954. The distribution of substance P and 5-hydroxytryptamine in the central nervous system of the dog. *J. Physiol. (Lond.)* 126: 596–618.
3. Chang, M.M., S.E. Leeman & H.D. Niall. 1971. Amino acid sequence of substance P. *Nat. New Biol.* 232: 86–87.
4. Tregear, G.W., H.D. Niall, J.T. Potts Jr., *et al.* 1971. Synthesis of substance P. *Nat. New Biol* 232: 87–89.
5. Fong, T.M., S.A. Anderson, H. Yu, *et al.* 1992. Differential activation of intracellular effector by two isoforms of human neurokinin-1 receptor. *Mol. Pharm.* 41: 24–30.
6. Snider, R.M., J.W. Constantine, J.A. Lowe, *et al.* 1991. A potent nonpeptide antagonist of the substance P (NK1) receptor. *Science* 251: 435–437.
7. Bountra, C., K. Bunce, T. Dale, *et al.* 1993. Antiemetic profile of a non-peptide neurokinin NK 1 receptor antagonist, CP-99,994, in ferrets. *Eur. J. Pharmacol.* 249: R3–R4.
8. Tattersall, F.D., W. Rycroft, R.J. Hargreaves, *et al.* 1993. The tachykinin NK_1 receptor antagonist CP99,994 attenuates cisplatin induced emesis in the ferret. *Eur. J. Pharmacol.* 250: R5–R6.
9. Watson, J.W., J.F. Gonsalves, A.A. Fossa, *et al.* 1995. The antiemetic effects of CP-99,994 in the ferret and the dog: role of the NK_1 receptor. *Br. J. Pharmacol.* 115: 84–94.
10. Andrews, P.L.R. & J.A. Rudd. 2004. The role of tachykinins and the tachykinin NK1 receptor in nausea and emesis. In *Handbook of Experimental Pharmacology*. P. Holzer, Ed.: 359–440. Springer. New York.
11. Tattersall, F.D., W. Rycroft, M. Cumberbatch, *et al.* 2000. The novel NK_1 receptor antagonist L-754,030 and its water soluble phosphoryl prodrug L-758,298 inhibit acute and delayed cisplatin-induced emesis in ferrets. *Neuropharmacology* 39: 652–663.
12. Tattersall, F.D., W. Rycroft & B. Francis. 1996. Tachykinin NK_1 receptor antagonists act centrally to inhibit emesis induced by the chemotherapeutic agent cisplatin in ferrets. *Neuropharmacology* 35: 1121–1129.
13. Hale, J.J., S.G. Mills, M. MacCoss, *et al.* 1998. Structural optimization affording 2-(R)-(1-(R)-3, 5-bis (trifluoromethyl) phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-oxo-1,2,4-triazol-5yl) methylmorpholine, a potent orally active, long-acting morpholine acetal human NK_1 receptor antagonist. *J. Med. Chem.* 41: 4607–4614.
14. Frank, R. & R. Hargreaves. 2003. Clinical biomarkers in drug discovery and development. *Nat. Rev. Drug Discov.* 2: 566–580.
15. Bergström, M., R.J. Hargreaves, H.D. Burns, *et al.* 2004. Human positron emission tomography studies of brain neurokinin 1 receptor occupancy by aprepitant. *Biol. Psychiatry* 55: 1007–1012.
16. Brands, K.M.J., J.F. Payack, J.D. Rosen, *et al.* 2003. Efficient synthesis of NK1 receptor antagonist aprepitant using a crystallization-induced diastereoselective transformation. *J. Am. Chem. Soc.* 125: 2129–2135.
17. Olver, I., S. Shelukar & K.C. Thompson. 2007. Nanomedicines in the treatment of emesis during chemotherapy: focus on aprepitant. *Int. J. Nanomedicine.* 2: 13–18.
18. Hale, J.J., S.G. Mills, M. MacCoss, *et al.* 2000. Phosphorylated morpholine acetal human neurokinin-1 receptor antagonists as water soluble prodrugs. *J. Med. Chem.* 43: 1234–1241.
19. Cocquyt, V., S. Van Belle, R.R. Reinhardt, *et al.* 2001. Comparison of L-758,298, a prodrug for the selective neurokinin-1 antagonist, L-754,030, with ondansetron for the prevention of cisplatin-induced emesis. *Eur. J. Cancer* 37: 835–842.
20. Chawla, S.P., S.M. Grunberg, R.J. Gralla, *et al.* 2003. Establishing the dose of the oral NK1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting. *Cancer* 97: 2290–2300.
21. Poli-Bigelli, S., J. Rodrigues-Pereira, A.D. Carides, *et al.* Aprepitant Protocol 054 Study Group. 2003. Addition of the neurokinin 1 receptor antagonist aprepitant to standard antiemetic therapy improves control of chemotherapy-induced nausea and vomiting. Results from a randomized, double-blind, placebo-controlled trial in Latin America. *Cancer* 97: 3090–3098.
22. Hesketh, P.J., S.M. Grunberg, R.J. Gralla, *et al.* Aprepitant Protocol 052 Study Group. 2003. The oral neurokinin-1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting: a multinational, randomized, double-blind, placebo-controlled trial in patients receiving high-dose cisplatin—the Aprepitant Protocol 052 Study Group. *J. Clin. Oncol.* 21: 4112–4119.
23. Herrstedt, J., H.B. Muss, D.G. Warr, *et al.* Aprepitant Moderately Emetogenic Chemotherapy Study Group. 2005. Efficacy and tolerability of aprepitant for the prevention of chemotherapy-induced nausea and emesis over multiple cycles of moderately emetogenic chemotherapy. *Cancer* 104: 1548–1555.
24. Warr, D.G., P.J. Hesketh, R.J. Gralla, *et al.* 2005. Efficacy and tolerability of aprepitant for the prevention of chemotherapy-induced nausea and vomiting in patients with breast cancer after moderately emetogenic chemotherapy. *J. Clin. Oncol.* 23: 2822–2830.
25. Grote, T., J. Hajdenberg, A. Cartmell, *et al.* 2006. Combination therapy for chemotherapy-induced nausea and vomiting in patients receiving moderately emetogenic chemotherapy: palonosetron, dexamethasone, and aprepitant. *J. Support. Oncol.* 4: 403–408.
26. de Wit, R., J. Herrstedt, B. Rapoport, *et al.* 2004. The oral $NK(_1)$ antagonist, aprepitant, given with standard antiemetics provides protection against nausea and vomiting over multiple cycles of cisplatin-based chemotherapy: a combined analysis of two randomised, placebo-controlled phase III clinical trials. *Eur. J. Cancer* 40: 403–410.
27. George, E., C. Hornuss & C.C. Apfel. 2010. Neurokinin-1 and novel serotonin antagonists for postoperative and

postdischarge nausea and vomiting. *Curr. Opin. Anesthesiol.* 23: 714–721.
28. Gan, T.J., C.C. Apfel, A. Kovac, *et al.* 2007. A randomized, double-blind comparison of the NK1 antagonist, aprepitant, versus ondansetron for the prevention of postoperative nausea and vomiting. *Anesth. Analg.* 104: 1082–1089.
29. Hornby, P.J. 2001. Central neurocircuitry associated with emesis. *Am. J. Med.* 111: 106S–112S.
30. Hesketh, P.J., S. Van Belle, M. Aapro, *et al.* 2003. Differential involvement of neurotransmitters through the time course of cisplatin-induced emesis as revealed by therapy with specific receptor antagonists. *Eur. J. Cancer* 39: 1074–1080.
31. Pendergrass, K., R.J. Hargreaves, K.J. Petty, *et al.* 2004. Aprepitant. An oral NK1 antagonist for the prevention of nausea and vomiting induced by highly emetogenic chemotherapy. *Drugs Today* 40: 853–863.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
092459-0171		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US2015/051050	18 September 2015 (18-09-2015)	19 September 2014 (19-09-2014)
Applicant		
HERON THERAPEUTICS, INC.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language,** the international search was carried out on the basis of:

[X] the international application in the language in which it was filed

[ ] a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

b. [ ] This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).

c. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [ ] **Certain claims were found unsearchable** (See Box No. II)

3. [ ] **Unity of invention is lacking** (see Box No III)

4. With regard to the **title,**

[X] the text is approved as submitted by the applicant

[ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

[X] the text is approved as submitted by the applicant

[ ] the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings,**

a. the figure of the **drawings** to be published with the abstract is Figure No. _____

[ ] as suggested by the applicant

[ ] as selected by this Authority, because the applicant failed to suggest a figure

[ ] as selected by this Authority, because this figure better characterizes the invention

b. [X] none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2015/051050

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/00 A61K47/10 A61K47/44 A61K47/24 A61K47/12 A61K47/26
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2014/005606 A1 (PHARMATHEN SA [GR]; KARAVAS EVANGELOS [GR]; KOUTRIS EFTHIMOS [GR]; BIK) 9 January 2014 (2014-01-09) the whole document claim 1; table 9 -----	1-17
X	WO 2013/177501 A2 (INNOPHARMA INC [US]) 28 November 2013 (2013-11-28) the whole document paragraph [0032]; claims 1,2 -----	1-17
X	WO 2011/158053 A1 (NANOFORM CARDIOVASCULAR THERAPEUTICS LTD [GB]; FILIPCSEI GENOVEVA [HU]) 22 December 2011 (2011-12-22) the whole document example 5 ----- -/--	1-17

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 December 2015	18/12/2015

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Giese, Hans-Hermann

1

Form PCT/ISA/210 (second sheet) (April 2005)

International application No
PCT/US2015/051050

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CN 102 379 845 A (NANJING YOKO BIOLOG MEDICAL CO LTD) 21 March 2012 (2012-03-21) the whole document claim 1; example 1	1-17
A	WO 2005/016308 A1 (CHEN ANDREW XIAN [US]) 24 February 2005 (2005-02-24) claims; examples 6,8	1
A	WO 2009/124756 A1 (EUROPEAN MOLECULAR BIOLOGY LAB EMBL [DE]; UNIV MODENA E REGGIO EMILIA) 15 October 2009 (2009-10-15) the whole document	1

1

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2014005606 A1	09-01-2014	EP 2866797 A1	06-05-2015
		US 2015165045 A1	18-06-2015
		WO 2014005606 A1	09-01-2014
WO 2013177501 A2	28-11-2013	AU 2013266141 A1	11-12-2014
		CA 2874700 A1	28-11-2013
		CN 104619312 A	13-05-2015
		EP 2855436 A2	08-04-2015
		HK 1203193 A1	23-10-2015
		IL 235864 A	01-02-2015
		JP 2015521190 A	27-07-2015
		KR 20150022839 A	04-03-2015
		SG 11201407765V A	29-01-2015
		US 2013317016 A1	28-11-2013
		WO 2013177501 A2	28-11-2013
WO 2011158053 A1	22-12-2011	AU 2011266808 A1	07-02-2013
		CN 103097379 A	08-05-2013
		EP 2582697 A1	24-04-2013
		JP 2013528642 A	11-07-2013
		RU 2013102030 A	27-07-2014
		SG 186377 A1	30-01-2013
		US 2013209521 A1	15-08-2013
		WO 2011158053 A1	22-12-2011
CN 102379845 A	21-03-2012	NONE	
WO 2005016308 A1	24-02-2005	CA 2576060 A1	24-02-2005
		EP 1651186 A1	03-05-2006
		JP 2007501253 A	25-01-2007
		US 2005049209 A1	03-03-2005
		WO 2005016308 A1	24-02-2005
WO 2009124756 A1	15-10-2009	NONE	

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
092459-0175		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US2016/015992	1 February 2016 (01-02-2016)	
Applicant		
HERON THERAPEUTICS, INC.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language,** the international search was carried out on the basis of:
      [X] the international application in the language in which it was filed
      [ ] a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. [ ] This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [ ] **Certain claims were found unsearchable** (See Box No. II)

3. [ ] **Unity of invention is lacking** (see Box No III)

4. With regard to the **title,**
   [ ] the text is approved as submitted by the applicant
   [X] the text has been established by this Authority to read as follows:

   EMULSION COMPRISING AN NK-1 RECEPTOR ANTAGONIST

5. With regard to the **abstract,**
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings,**
   a. the figure of the **drawings** to be published with the abstract is Figure No. _____
      [ ] as suggested by the applicant
      [ ] as selected by this Authority, because the applicant failed to suggest a figure
      [ ] as selected by this Authority, because this figure better characterizes the invention
   b. [X] none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2016/015992

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/00 A61K47/24 A61K9/107 A61K31/454 A61K31/496 A61K31/5377
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2016/024092 A1 (WAN JIANSHENG [US] ET AL) 28 January 2016 (2016-01-28)	18-25
A	figure 3 paragraph [0004] examples 1-7	1-17, 26-28
A	CN 102 379 845 A (NANJING YOKO BIOLOG MEDICAL CO LTD) 21 March 2012 (2012-03-21) the whole document	1-28
A	US 2013/317016 A1 (HINGORANI TUSHAR [US] ET AL) 28 November 2013 (2013-11-28) paragraph [0054] - paragraph [0056]	1-28
A	WO 2014/209962 A1 (TIGERCAT PHARMA INC [US]) 31 December 2014 (2014-12-31) example 4 table 7	1-28

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[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents :

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"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
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Date of the actual completion of the international search	Date of mailing of the international search report
24 May 2016	03/06/2016

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Sindel, Ulrike

1

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2014/005606 A1 (PHARMATHEN SA [GR]; KARAVAS EVANGELOS [GR]; KOUTRIS EFTHIMOS [GR]; BIK) 9 January 2014 (2014-01-09) claims 1-3	1-28
E	WO 2016/044784 A1 (HERON THERAPEUTICS INC [US]) 24 March 2016 (2016-03-24) claims 1-17	1-9, 11-16, 18-23, 26-28

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2016/015992

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2016024092 A1	28-01-2016	AU 2010282483 A1	01-03-2012
		BR 112012003263 A2	22-09-2015
		CA 2770403 A1	17-02-2011
		CN 102573475 A	11-07-2012
		CN 105503870 A	20-04-2016
		EP 2464230 A1	20-06-2012
		JP 5860399 B2	16-02-2016
		JP 2013501806 A	17-01-2013
		JP 2016041734 A	31-03-2016
		KR 20120060215 A	11-06-2012
		RU 2012109405 A	20-09-2013
		SG 178403 A1	29-03-2012
		SG 10201407538W A	29-01-2015
		TW 201111382 A	01-04-2011
		TW 201604195 A	01-02-2016
		US 2011038925 A1	17-02-2011
		US 2016024092 A1	28-01-2016
		WO 2011019911 A1	17-02-2011
CN 102379845 A	21-03-2012	NONE	
US 2013317016 A1	28-11-2013	AU 2013266141 A1	11-12-2014
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		CN 104619312 A	13-05-2015
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		HK 1203193 A1	23-10-2015
		JP 2015521190 A	27-07-2015
		KR 20150022839 A	04-03-2015
		NZ 702114 A	26-02-2016
		SG 11201407765V A	29-01-2015
		US 2013317016 A1	28-11-2013
		WO 2013177501 A2	28-11-2013
WO 2014209962 A1	31-12-2014	AU 2014302694 A1	07-01-2016
		CA 2915474 A1	31-12-2014
		CN 105473138 A	06-04-2016
		EP 3013336 A1	04-05-2016
		KR 20160023692 A	03-03-2016
		PH 12015502777 A1	21-03-2016
		WO 2014209962 A1	31-12-2014
WO 2014005606 A1	09-01-2014	EP 2866797 A1	06-05-2015
		US 2015165045 A1	18-06-2015
		WO 2014005606 A1	09-01-2014
WO 2016044784 A1	24-03-2016	US 2016082013 A1	24-03-2016
		WO 2016044784 A1	24-03-2016

Form PCT/ISA/210 (patent family annex) (April 2005)

Information on Search Strategy - Pilot phase (see OJ 2015, A86)
The type of information contained in this sheet may change during the pilot for improving the usefulness of this new service.

Application Number
PCT/US2016/015992

TITLE: EMULSION COMPRISING AN NK-1 RECEPTOR ANTAGONIST

APPLICANT: HERON THERAPEUTICS, INC.

IPC CLASSIFICATION: A61K9/00, A61K47/24, A61K9/107, A61K31/454, A61K31/496, A61K31/5377

EXAMINER: Sindel, Ulrike

CONSULTED DATABASES:

CLASSIFICATION SYMBOLS DEFINING EXTENT OF THE SEARCH:

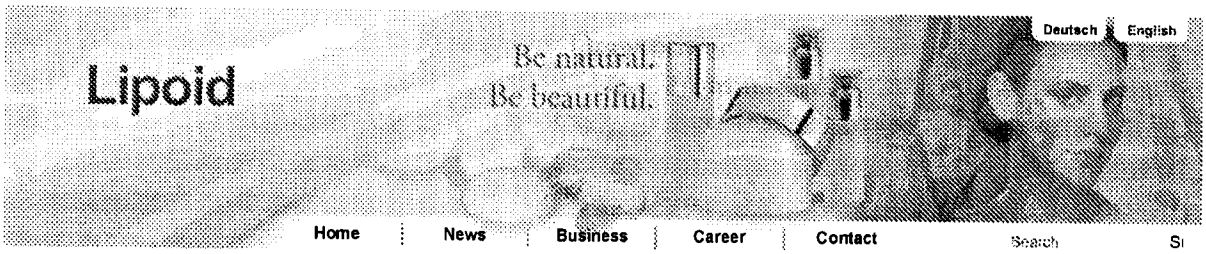
IPC:

CPC: A61K9/0019, A61K47/24, A61K9/1075, A61K31/454, A61K31/496, A61K31/5377

FI/F-TERMS:

KEYWORDS OR OTHER ELEMENTS FEATURING THE INVENTION:

EPO FORM P04A42



Lipoid Kosmetik

Applications

Pharmaceutical Industry

Cosmetic Industry

Dietetics Industry

Products

Lecithin

Phospholipids

Compounds with Phosphatidylcholine

Delivery Systems

Liposomes

Special Products

Our Brands

LIPOID

PHOSPHOLIPON®

PHOSAL®

PhytoSolve®

Ultraspheres®

Product Finder

LIPOID Brand Name	**E** Source: Egg	**80** Approx. Percentage of Phosphatidylcholine	
LIPOID Brand Name	**S** Source: Soybean	**100** Approx. Percentage of Phosphatidylcholine	
LIPOID Brand Name	**S** Source: Soybean	**PC** Pure Phosphatidylcholine	**3** Max. Iodine Value
LIPOID Brand Name	**PC** Pure Phosphatidylcholine	**14:0** Pos. 1: Number of Carbon Atoms: Number of Double Bonds	**14:0** Pos. 2: Number of Carbon Atoms: Number of Double Bonds
PHOSPHOLIPON® Brand Name	Source: Soybean	**85** Approx. Percentage of Phosphatidylcholine	**G** Granular Product
PHOSPHOLIPON® Brand Name	Source: Soybean	**80** Approx. Percentage of Phosphatidylcholine	**H** Hydrogenated
PHOSPHOLIPON® Brand Name	**R** Source: Rapeseed	**LPC** Lysophosphatidylcholine	**20** Approx. Percentage of Lysophosphatidylcholine
PHOSAL® Brand Name	**53** Approx. Percentage of Phosphatidylcholine	**MCT** Carrier Ingredient Composition	
LIPOID Brand Name	**GPC** Glycerophosphocholine	**85** Approx. Percentage of Glycerophosphocholine	**F** Fluid
PhytoSolve®	**Delivery System**		

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Product Finder

LIPOID	E	80	
Brand Name	Source: Egg	Approx. Percentage of Phosphatidylcholine	
LIPOID	S	100	
Brand Name	Source: Soybean	Approx. Percentage of Phosphatidylcholine	
LIPOID	S	PC	3
Brand Name	Source: Soybean	Pure Phosphatidylcholine	Max. Iodine Value
LIPOID	PC	14:0	14:0
Brand Name	Pure Phosphatidylcholine	Pos. 1: Number of Carbon Atoms: Number of Double Bonds	Pos. 2: Number of Carbon Atoms: Number of Double Bonds
PHOSPHOLIPON®		85	G
Brand Name	Source: Soybean	Approx. Percentage of Phosphatidylcholine	Granular Product
PHOSPHOLIPON®		80	H
Brand Name	Source: Soybean	Approx. Percentage of Phosphatidylcholine	Hydrogenated
PHOSPHOLIPON®	R	LPC	20
Brand Name	Source: Rapeseed	Lysophosphatidylcholine	Approx. Percentage of Lysophosphatidylcholine
PHOSAL®	53	MCT	
Brand Name	Approx. Percentage of Phosphatidylcholine	Carrier Ingredient Composition	
LIPOID	GPC	85	F
Brand Name	Glycerophosphocholine	Approx. Percentage of Glycerophosphocholine	Fluid

PhytoSolve® Delivery System

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REDUCTION OF CISPLATIN-INDUCED EMESIS BY A SELECTIVE NEUROKININ-1–RECEPTOR ANTAGONIST

RUDOLPH M. NAVARI, M.D., RICK R. REINHARDT, M.D., PH.D., RICHARD J. GRALLA, M.D., MARK G. KRIS, M.D., PAUL J. HESKETH, M.D., ALI KHOJASTEH, M.D., HEDY KINDLER, M.D., THOMAS H. GROTE, M.D., KELLY PENDERGRASS, M.D., STEVEN M. GRUNBERG, M.D., ALEXANDRA D. CARIDES, PH.D., AND BARRY J. GERTZ, M.D., PH.D., FOR THE L-754,030 ANTIEMETIC TRIALS GROUP*

ABSTRACT

Background The localization of substance P in brain-stem regions associated with vomiting, and the results of studies in ferrets, led us to postulate that a neurokinin-1–receptor antagonist would be an antiemetic in patients receiving anticancer chemotherapy.

Methods In a multicenter, double-blind, placebo-controlled trial involving 159 patients who had not previously received cisplatin, we evaluated the prevention of acute emesis (occurring within 24 hours) and delayed emesis (occurring on days 2 to 5) after a single dose of cisplatin therapy (70 mg or more per square meter of body-surface area). Before receiving cisplatin, all the patients received granisetron (10 μg per kilogram of body weight intravenously) and dexamethasone (20 mg orally). The patients were randomly assigned to one of three treatments in addition to granisetron and dexamethasone: 400 mg of an oral trisubstituted morpholine acetal (also known as L-754,030) before cisplatin and 300 mg on days 2 to 5 (group 1), 400 mg of L-754,030 before cisplatin and placebo on days 2 to 5 (group 2), or placebo before cisplatin and placebo on days 2 to 5 (group 3). Additional medication was available at any time to treat occurrences of vomiting or nausea.

Results In the acute-emesis phase, 93 percent of the patients in groups 1 and 2 combined and 67 percent of those in group 3 had no vomiting ($P<0.001$). In the delayed-emesis phase, 82 percent of the patients in group 1, 78 percent of those in group 2, and 33 percent of those in group 3 had no vomiting ($P<0.001$ for the comparison between group 1 or 2 and group 3). The median nausea score in the delayed-emesis phase was significantly lower in group 1 than in group 3 ($P=0.003$). No serious adverse events were attributed to L-754,030.

Conclusions The neurokinin-1–receptor antagonist L-754,030 prevents delayed emesis after treatment with cisplatin. Moreover, combining L-754,030 with granisetron plus dexamethasone improves the prevention of acute emesis. (N Engl J Med 1999;340: 190-5.)

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PATIENTS consistently report that vomiting and nausea are among the most unpleasant and distressing aspects of chemotherapy.[1] Vomiting due to anticancer drugs reduces the quality of life[2] and may cause patients to delay or refuse potentially curative therapy.[3]

The severity and pattern of chemotherapy-induced emesis depend on the specific agents used, the dose, and the regimen.[4] Cisplatin is most commonly associated with profound nausea and vomiting, which follow a distinct pattern of an acute phase (within 24 hours after chemotherapy) and a delayed phase (on days 2 to 5).[5] Severe acute emesis occurs in virtually all patients who receive doses of cisplatin of $\geq$50 mg per square meter of body-surface area without prophylactic antiemetics[6]; delayed emesis occurs in 57 to 89 percent, with maximal intensity on days 2 and 3 after chemotherapy.[7-11]

Efforts to prevent chemotherapy-induced emesis have been directed at blocking neurotransmitter receptors in the brain-stem vomiting center. The chemoreceptor trigger zone in the area postrema transmits impulses to the vomiting center after the administration of chemotherapeutic agents.[12] Receptors for neurotransmitters such as dopamine, endorphin, serotonin, and substance P are found in these areas. Initial efforts focused on blocking dopamine with phenothiazines, butyrophenones, and metoclopramide (which was later found to bind the serotonin receptor).[13] Each compound is partially effective when given as a single agent. Combinations of antiemetics, such as metoclopramide plus dexamethasone, were found to improve the prevention of chemotherapy-induced emesis significantly.[14] The next major breakthrough occurred with the introduction of selective serotonin antagonists, such as ondansetron and granisetron, which have peripheral and central sites of action.

Although serotonin antagonists by themselves improve the prevention of acute chemotherapy-induced emesis,[15-17] better control is achieved with the combination of a serotonin antagonist and dexamethasone, which completely prevents vomiting in 48 to 91 percent of patients.[18-20] However, the serotonin antagonists are not as effective against delayed emesis.[21,22] The most effective current approach to the prevention of delayed emesis is the combination of a serotonin antagonist or metoclopramide with dexameth-

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*Other members of the L-754,030 Antiemetic Trials Group are listed in the Appendix.

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asone, which completely prevents delayed emesis in 52 to 69 percent of patients.[9,23] These regimens require multiple daily doses, and metoclopramide can cause sedation and extrapyramidal side effects. Thus, there is considerable opportunity for improvement in the prevention of delayed emesis.

Substance P is one of four mammalian tachykinins found in neurons, including vagal afferent fibers innervating the brain-stem nucleus tractus solitarii and area postrema. Exogenous substance P applied to cells in the nucleus tractus solitarii causes vomiting.[24] The biologic actions of substance P are mediated through the neurokinin-1 receptor, a G-protein receptor coupled to the inositol phosphate signal-transduction pathway.[25]

L-754,030, a trisubstituted morpholine acetal, is a potent and selective nonpeptide neurokinin-1–receptor antagonist. Neurokinin-1–receptor antagonists inhibit emesis induced by cisplatin in ferrets, and central nervous system penetration is essential for the antiemetic activity of the drug.[26-28] In ferrets, L-754,030 resulted in a dose-dependent inhibition of both acute and delayed cisplatin-induced vomiting.[29] Moreover, additive efficacy was achieved by combining L-754,030 with either dexamethasone or ondansetron (Tattersall FD: personal communication). Preliminary observations suggested that similar benefits might be obtained with a neurokinin-1–receptor antagonist in patients.[30]

We undertook this study to evaluate a neurokinin-1–receptor antagonist, L-754,030, for the prevention of delayed emesis due to cisplatin; to determine whether L-754,030 enhances the acute antiemetic effect of the combination of a serotonin antagonist and dexamethasone; and to assess the safety of L-754,030.

METHODS

Study Design

The subjects of this double-blind, multicenter, placebo-controlled study were men and women with cancer who had not previously been treated with cisplatin. The patients were assigned to one of three treatment groups according to a computer-generated randomization schedule that incorporated stratification according to sex and according to whether or not the patient was receiving additional highly emetogenic therapy, as previously defined.[31] All the patients provided written informed consent.

In all three groups, the patients received an oral dose of dexamethasone (20 mg) and an intravenous dose of granisetron (10 μg per kilogram of body weight) 30 minutes before receiving a single dose of cisplatin (day 1). On day 1, the patients also received 400 mg of oral L-754,030 (groups 1 and 2) or placebo (group 3). The patients in group 1 also received 300 mg of L-754,030 once daily on days 2 through 5, whereas the patients in groups 2 and 3 received placebo on days 2 through 5. Rescue therapy for day 1 (20 to 30 mg of metoclopramide orally four times daily or 1 to 2 mg per kilogram intravenously four times daily) and days 2 to 5 (8 mg of dexamethasone orally twice daily with or without metoclopramide) was permitted at any time but was not given prophylactically. L-754,030 or placebo was given orally 2 hours before cisplatin infusion on day 1, approximately 24 hours after initiation of the cisplatin infusion on day 2, and on subsequent days between 8 and 10 a.m.

Eligibility

Patients were enrolled who were at least 18 years of age and who were scheduled to receive a first course of cisplatin at a dose of at least 70 mg per square meter. Women of child-bearing age had to have a negative test for the β subunit of human chorionic gonadotropin in serum. The primary exclusion criteria included a Karnofsky score of less than 60; allergy to or intolerance of metoclopramide, dexamethasone, or granisetron; therapy with another antiemetic drug (serotonin antagonists, phenothiazines, butyrophenones, cannabinoids, metoclopramide, or glucocorticoids) within 72 hours before day 1; an episode of vomiting or retching within 24 hours before the start of the cisplatin infusion; treatment for or history of a seizure within the previous two years; severe concurrent illness other than cancer; gastrointestinal obstruction or active peptic ulcer; radiation therapy to the abdomen or pelvis within one week before or after day 1; or any of the following laboratory measurements: hemoglobin level below 8.5 g per deciliter, white-cell count below 3500 per cubic millimeter, platelet count below 100,000 per cubic millimeter, serum aspartate aminotransferase level more than twice the upper limit of normal, serum alanine aminotransferase level more than twice the upper limit of normal, serum bilirubin level more than twice the upper limit of normal, serum alkaline phosphatase level more than twice the upper limit of normal, serum albumin level below 3 g per deciliter, and serum creatinine level of more than 2 mg per deciliter (180 μmol per liter). Five patients who were scheduled to receive paclitaxel in addition to cisplatin were permitted to receive additional glucocorticoids before day 1.

Assessments

Episodes of vomiting or retching were recorded by the patients on diary cards. An emetic episode was defined as a single instance of vomiting or retching, or any number of continuous instances of vomiting or retching; distinct episodes were separated by at least one minute. The primary measure of efficacy was the proportion of patients without emesis in the delayed-emesis phase.

Nausea was assessed on a 100-mm horizontal visual-analogue scale in the patient diary with the heading "How much nausea have you had over the past 24 hours?" The left-hand end of the scale (0 mm) was labeled "no nausea," and the right-hand end (100 mm) was labeled "nausea as bad as it could be." Every 24 hours the patient indicated the degree of nausea during the previous 24 hours by placing a vertical mark on the scale line.

Global satisfaction with the antiemetic treatment was assessed on a 100-mm visual-analogue scale on the mornings of days 2 and 6 after cisplatin treatment. The scale for day 2 was headed "How satisfied are you with your anti-emetic treatment over the past 24 hours?" The scale for day 6 was headed "How satisfied are you with your anti-emetic treatment over the entire study period?" On both scales, 0 mm was labeled "not at all satisfied," and 100 mm was labeled "completely satisfied."

Adverse events were recorded up to the post-study visit, which occurred between day 17 and day 29. The patients also underwent laboratory safety studies (hematologic, serum chemical, and urine analyses), electrocardiography, and physical examinations between days 6 and 8 and between days 17 and 29.

Statistical Analysis

The statistical analysis of efficacy was performed on an intention-to-treat basis (all patients with data on emesis after the administration of L-754,030 were included). The incidence of vomiting in the acute-emesis and delayed-emesis phases and the use of rescue medication in both phases were evaluated. Fisher's exact test was used for pairwise comparison of the incidence of emesis (and no emesis or use of rescue therapy) between treatment groups. The proportions of patients with one or two and with three or more emetic episodes in the delayed-emesis phase were also summarized. A Bonferroni adjustment for multiplicity was used in testing for significance only in the analysis of emesis, since

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TABLE 1. CHARACTERISTICS OF THE STUDY PATIENTS.*

CHARACTERISTIC	DAILY L-754,030 (GROUP 1)	SINGLE-DOSE L-754,030 (GROUP 2)	PLACEBO (GROUP 3)
No. of patients	54	54	51
Male sex (%)	65	65	59
Age (yr)	64±10	61±11	60±13
No. of alcoholic drinks/wk (%)†			
0–4	80	87	80
5–10	7	7	8
≥11	9	4	10
Cisplatin dose (mg/m²)	77±11	80±12	81±12
Additional emetogenic chemotherapy (%)	4	4	4
Type of cancer (%)			
Lung	68	69	68
Gastrointestinal	13	7	8
Head and neck	11	11	8
Genitourinary	4	11	8
Other	4	2	8

*Plus–minus values are means ±SD.

†Percentages do not total 100 because some data were missing.

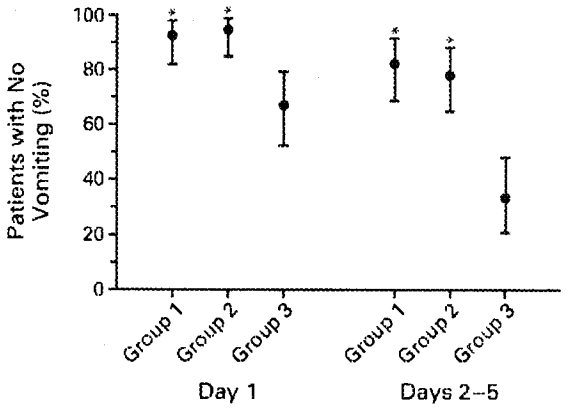


Figure 1. Percentage of Patients with No Vomiting during the Acute-Emesis (Day 1) and Delayed-Emesis (Days 2 to 5) Phases.

Bars indicate 95 percent confidence intervals. All groups received granisetron and dexamethasone before receiving cisplatin. In addition, group 1 received L-754,030 before cisplatin and on days 2 to 5; group 2 received L-754,030 before cisplatin and placebo on days 2 to 5; and group 3 received placebo before cisplatin and on days 2 to 5. Asterisks indicate $P<0.001$ for the comparisons with group 3.

emesis was the primary end point. Nominal 95 percent confidence intervals are reported. A sample size of 43 patients per group provided the study with 80 percent power to detect a 30 percentage point increase or a 25 percentage point decrease as compared with placebo in the proportion of patients without vomiting in the delayed-emesis phase (two-sided test, alpha=0.05).

A secondary measure of efficacy was the patient's self-assessment of nausea. In the analysis for days 1 to 5 and 2 to 5, an average score was calculated for each patient from the values on the visual-analogue scale over the given interval; the analysis for day 2 used the rating recorded on day 2. Because the distribution of values was not normal, nonparametric analyses were performed on the ranked scores. For days 1 to 5 and days 2 to 5, the distributions of these average scores were compared among the treatment groups with use of the Kruskal–Wallis chi-square test, and median values for these distributions are reported. Pairwise comparisons were also made with use of the Wilcoxon test. In addition, Fisher's exact test was used to make pairwise comparisons of the proportions of patients who had no nausea or minimal nausea (defined post hoc as a rating on the visual-analogue scale that averaged less than 5 mm over the entire period) on days 1 to 5, days 2 to 5, and day 2 only.

An exploratory measure was the patient's global degree of satisfaction with the antiemetic therapy. The groups were compared with use of a general linear model and a nonparametric analysis of the ranked scores. The results of the two analyses were similar, and the medians are reported.

RESULTS

Of the 159 patients who enrolled in this study, 1 patient in group 1 was excluded from both phases of the trial, because the patient vomited before the cisplatin infusion and no data on emesis were collected. Three others in group 1 were excluded from the analysis of the delayed-emesis phase; all three withdrew from the study and provided no data on emesis for the delayed-emesis phase, one because of inability to swallow the pills and two because of lack of efficacy in the acute phase. Two patients in group 3 received glucocorticoids during the study for reasons other than rescue medication but were included in the efficacy analysis. The base-line characteristics of the patients assigned to the three treatment groups were similar (Table 1).

Prevention of Vomiting

During the acute-emesis period, the treatment that best prevented vomiting was triple therapy with granisetron, dexamethasone, and L-754,030 (groups 1 and 2). The proportion of patients who did not vomit was significantly higher in group 1 (93 percent), group 2 (94 percent), and in groups 1 and 2 combined (93 percent) than in group 3, which received the standard therapy of granisetron and dexamethasone (67 percent, $P<0.001$ for the comparison between groups 1 and 2 combined and group 3) (Fig. 1). The difference in the proportions of patients with no emesis between groups 1 and 2 combined and group 3 was 26 percentage points (95 percent confidence interval, 12 to 43).

The proportions of patients who had no emesis and who did not require rescue therapy in group 1 (77 percent), group 2 (83 percent), and groups 1 and 2 combined (80 percent) were higher than that in group 3 (57 percent, $P=0.004$ for the comparison between groups 1 and 2 combined and group 3). The difference between groups 1 and 2 combined and group 3 in the proportion of patients who had no emesis and who did not require rescue therapy was 23 percentage points (95 percent confidence interval, 7 to 40).

During the delayed-emesis period, the prevention of emesis was best achieved in the patients who re-

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ceived L-754,030 (groups 1 and 2). The prevention of delayed emesis in groups 1 and 2 was significantly superior to that in group 3, in which placebo was given during both the acute- and delayed-emesis phases (the proportions of patients without delayed emesis in groups 1, 2, and 3 were 82 percent, 78 percent, and 33 percent, respectively; $P<0.001$ for the comparison between group 1 or 2 and group 3) (Fig. 1 and Table 2). The difference between groups 1 and 3 in the proportion of patients who did not vomit was 49 percentage points (95 percent confidence interval, 30 to 67); between groups 2 and 3, the difference was 45 percentage points (95 percent confidence interval, 26 to 62).

There were also significant differences between the groups receiving L-754,030 and the placebo group in the proportion of patients who had no emesis and did not require rescue therapy in the delayed-emesis phase (52 percent, 43 percent, and 16 percent in groups 1, 2, and 3, respectively; $P<0.001$ for the comparison between groups 1 and 3, and $P=0.003$ for the comparison between groups 2 and 3) (Table 2). These percentages corresponded to differences of 36 percentage points (95 percent confidence interval, 16 to 55) between groups 1 and 3 and 27 percentage points (95 percent confidence interval, 8 to 46) between groups 2 and 3. There was no significant difference between groups 1 and 2 in the proportion of patients with delayed emesis. The proportions of patients with no more than two episodes of delayed emesis were 98 percent in group 1, 93 percent in group 2, and 59 percent in group 3 ($P<0.001$ for the comparison between group 1 or 2 and group 3).

Assessment of Nausea

Figure 2 shows the median scores on the visual-analogue scale for nausea over time, and Table 3 gives these scores for days 1 to 5, days 2 to 5, and day 2. Over days 1 to 5 and days 2 to 5, the distribution of nausea scores was significantly lower in group 1 than in group 3 ($P=0.003$ for both comparisons). In the analysis for day 2, the nausea scores in groups 1 and 2 were significantly lower than those in group 3 ($P=0.002$ for group 1 vs. group 3, and $P=0.005$ for group 2 vs. group 3). The proportions of patients with no nausea or minimal nausea in groups 1, 2, and 3 on days 1 to 5 were 49 percent, 48 percent, and 25 percent, respectively ($P=0.02$ for group 1 vs. group 3, and $P=0.03$ for group 2 vs. group 3); on days 2 to 5, the proportions were 51 percent, 48 percent, and 24 percent, respectively ($P=0.007$ for group 1 vs. group 3, and $P=0.01$ for group 2 vs. group 3); and on day 2 the proportions were 65 percent, 61 percent, and 41 percent, respectively ($P=0.03$ for group 1 vs. group 3).

Assessment of Global Satisfaction

There was no difference among the treatment groups in the global-satisfaction rating on day 2 (the medians for groups 1 and 2 combined and for group 3 were both 100 mm). The median ratings on day 6 for global satisfaction in groups 1, 2, and 3 were 100, 98, and 82 mm, respectively. Groups 1 and 2 had significantly better ratings than group 3 ($P=0.001$ for group 1 vs. group 3, and $P=0.03$ for group 2 vs. group 3).

TABLE 2. FREQUENCY OF EPISODES OF VOMITING DURING THE DELAYED-EMESIS PHASE (DAYS 2 TO 5).

TREATMENT GROUP*	NO. OF PATIENTS	NO. OF EPISODES			NO EMESIS AND NO RESCUE THERAPY
		0	1–2	≥3	
		% of patients			
Daily L-754,030 (group 1)	50	82†	16	2	52‡
Single-dose L-754,030 (group 2)	54	78†	15	7	43‡
Placebo (group 3)	51	33	26	41	16

*All the patients received granisetron and dexamethasone on day 1.

†$P<0.001$ for the comparison with group 3.

‡$P<0.001$ for the comparison between groups 1 and 3, and $P=0.003$ for the comparison between groups 2 and 3.

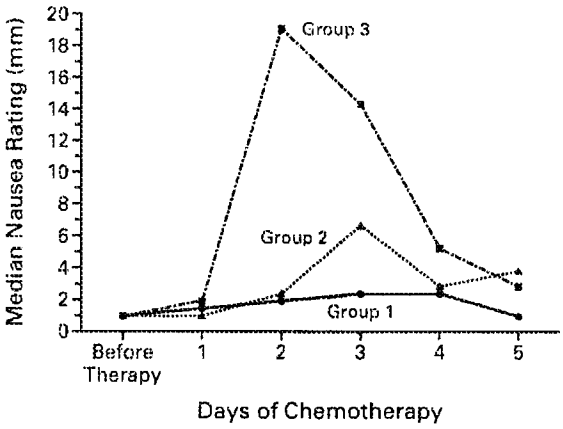


Figure 2. Median Scores on the Visual-Analogue Scale for Nausea during the Acute-Emesis (Day 1) and Delayed-Emesis (Days 2 to 5) Phases.

All groups received granisetron and dexamethasone before receiving cisplatin. In addition, group 1 received L-754,030 before cisplatin and on days 2 to 5; group 2 received L-754,030 before cisplatin and placebo on days 2 to 5; and group 3 received placebo before cisplatin and on days 2 to 5. The visual-analogue rating scale for nausea runs from 0 mm ("no nausea") to 100 mm ("nausea as bad as it could be"). The values for group 1 were significantly different from those for group 3 on days 1 to 5 and on days 2 to 5 ($P=0.003$ for both comparisons). The values for groups 1 and 2 were significantly different from those for group 3 on day 2 ($P=0.002$ for group 1 vs. group 3, and $P=0.005$ for group 2 vs. group 3).

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TABLE 3. MEDIAN SCORES ON THE VISUAL-ANALOGUE SCALE FOR NAUSEA DURING THE ACUTE-EMESIS AND DELAYED-EMESIS PHASES.*

TREATMENT GROUP†	ACUTE (DAY 1)	ACUTE AND DELAYED (DAYS 1–5)	DELAYED (DAYS 2–5)	DELAYED (DAY 2)
Daily L-754,030 (group 1)	0	1‡	1‡	1§
Single-dose L-754,030 (group 2)	0	2	3	2§
Placebo (group 3)	1	5	10	19

*The scale runs from 0 mm ("no nausea") to 100 mm ("nausea as bad as it could be").

†All the patients received granisetron and dexamethasone on day 1.

‡P=0.003 for the comparison with group 3.

§P=0.002 for the comparison between groups 1 and 3, and P=0.005 for the comparison between groups 2 and 3.

TABLE 4. MOST COMMON CLINICAL AND LABORATORY ADVERSE EVENTS.*

EVENT	DAILY L-754,030 (GROUP 1)	SINGLE-DOSE L-754,030 (GROUP 2)	PLACEBO (GROUP 3)
	number of patients (percent)		
Clinical events			
Constipation	10 (19)	7 (13)	9 (18)
Diarrhea	9 (17)	4 (7)	5 (10)
Dehydration	3 (6)	3 (6)	7 (14)
Headache	12 (22)	9 (17)	10 (20)
Hiccups	8 (15)	9 (17)	7 (14)
Asthenia	14 (26)	14 (26)	13 (25)
Hematologic changes†			
Decrease in total white-cell count	1 (2)	1 (2)	1 (2)
Decrease in neutrophils	0	1 (2)	1 (2)
Serum aminotransferase elevations‡			
Aspartate aminotransferase	0	0	4 (8)
Alanine aminotransferase	5 (9)	0	7 (14)

*All adverse events occurring on days 1 to 7 are listed, regardless of their relation to the study drugs. There were 54 patients in group 1, 54 in group 2, and 51 in group 3. All the patients received granisetron and dexamethasone on day 1.

†Listed are transient decreases in the white-cell count to less than 2000 per cubic millimeter and in neutrophils to less than 1000 per cubic millimeter in patients who had normal or above-normal base-line values (National Cancer Institute toxicity grade III or IV).[32]

‡Listed are transient increases to greater than 2.5 times the upper limit of the normal range in patients who had normal or below-normal base-line values (National Cancer Institute toxicity grade II, III, or IV).[32]

Safety

All 159 patients who received study medication were included in the analysis of safety. Table 4 lists the most common adverse events through day 7. There were no significant differences in the incidence of these events among the three groups, nor were significant differences observed with respect to laboratory indexes of safety. The same pattern in clinical and laboratory adverse events emerged when the entire study period (day 1 through the last study visit between days 17 and 29) was considered, and there were no significant differences among the treatment groups.

DISCUSSION

The use of serotonin antagonists in combination with dexamethasone has greatly reduced the frequency of acute chemotherapy-induced emesis but has had less effect on delayed nausea and vomiting caused by highly emetogenic agents such as cisplatin.[18-23] The results of our trial demonstrate that the standard therapy (granisetron plus dexamethasone) with the addition of the selective neurokinin-1 antagonist L-754,030 is superior to the standard therapy alone in preventing acute emesis, and that L-754,030 significantly reduces the frequency of vomiting and nausea in the delayed-emesis phase.

During the acute-emesis phase, the addition of L-754,030 to granisetron plus dexamethasone increased the proportion of patients who did not vomit by 26 percentage points. In addition, significantly fewer patients used rescue medication in the triple-therapy group. In the standard-therapy group, 67 percent of the patients did not vomit, a result similar to those of previous trials. In this group, 57 percent of the patients did not vomit and did not require rescue therapy, a result that may reflect the high expectations patients now have for control of nausea and vomiting, resulting in a lower threshold for rescue therapy.[33-35]

The proportion of patients with no delayed emesis in the groups given a single dose of L-754,030 on day 1 (group 2) or daily doses of L-754,030 (group 1) was approximately 50 percentage points greater than that in the group given placebo (group 3) and was up to 30 percentage points greater than the proportions reported with the most successful complex dual-therapy regimens (52 to 69 percent of patients given serotonin antagonists or metoclopramide with dexamethasone have no emesis).[9,23] In addition, significantly fewer patients used rescue medication when receiving multiple or single doses of L-754,030.

In the acute-emesis phase, triple therapy did not significantly reduce the frequency of nausea as compared with standard therapy. However, the group receiving daily L-754,030 had significantly less nausea in the delayed-emesis phase and over the entire study period than the placebo group. In addition, the global satisfaction of patients with their antiemetic therapy was significantly greater with L-754,030. Use of L-754,030 should improve patients' quality of life, because nausea now outranks vomiting as the most unpleasant aspect of chemotherapy.[1]

During the delayed-emesis phase, the groups receiving single-dose therapy (group 2) and daily therapy (group 1) with L-754,030 did not differ significantly from each other in the proportion of patients who had no emesis. However, as compared with group 2, group 1 consistently had more patients who

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had no emesis and did not require rescue therapy, lower nausea scores, and higher global-satisfaction scores. Only a larger trial can determine whether continuation of L-754,030 treatment beyond day 1 yields an improvement that is both clinically and statistically significant. An argument could be made for testing the continuation of L-754,030 therapy at least through day 3, encompassing the period during which the incidence and severity of delayed nausea and vomiting are greatest.

L-754,030 (in either single or multiple doses) was generally well tolerated, with an incidence of clinical and laboratory adverse events that was similar to that with placebo.

In summary, the addition of L-754,030 to granisetron and dexamethasone treatment before chemotherapy provided better protection against vomiting in the acute-emesis phase than the combination of dexamethasone and a serotonin antagonist alone. Moreover, single and multiple doses of L-754,030 prevented delayed emesis after high-dose cisplatin therapy. A neurokinin-1–receptor antagonist such as L-754,030 represents a new type of agent acting through a novel mechanism to prevent vomiting in patients receiving highly emetogenic chemotherapy for cancer.

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APPENDIX

The other members of the L-754,030 Antiemetic Trials Group were F.A. Bailey and J. Hankins, SORRA Research Center, Birmingham, Ala.; F.P. Arena and H. Gerstein, Great Neck, N.Y.; S. Luedke, St. Louis Center for Clinical Research, St. Louis; S.J. Yee, Arcadia, Calif.; M. Modiano, Arizona Clinical Research, Tucson; D.F. Roychowdhury, University of Cincinnati, Cincinnati; R.C. Shepard, Medical West Oncology, Chicopee, Mass.; D.P. Gray, Columbus Regional Hospital Cancer Care, Columbus, Ind.; J.A. Reeves, Leecoast Research Center, Fort Myers, Fla.; I. Royston, Sidney Kimmel Cancer Center, San Diego, Calif.; J. Scott, Georgia Cancer Specialists, Decatur; C.J. Badolato, Associated Medical Research, Melbourne, Fla.; and W.R. Edwards, Rockford Clinic, Rockford, Ill.

REFERENCES

1. Griffin AM, Butow PN, Coates AS, et al. On the receiving end. V. Patient perceptions of the side effects of cancer chemotherapy in 1993. Ann Oncol 1996;7:189-95.
2. Osoba D, Zee B, Warr D, Kaizer L, Latreille J, Pater J. Quality of life studies in chemotherapy-induced emesis. Oncology 1996;53:Suppl 1:92-5.
3. Laszlo J, Lucas VS Jr. Emesis as a critical problem in chemotherapy. N Engl J Med 1981;305:948-9.
4. Gralla RJ. Controlling emesis in patients receiving cancer chemotherapy. Recent Results Cancer Res 1991;121:68-85.
5. Gralla RJ, Tyson LB, Kris MG, Clark RA. The management of chemotherapy-induced nausea and vomiting. Med Clin North Am 1987;71:289-301.
6. Kris MG, Cubeddu LX, Gralla RJ, et al. Are more antiemetic trials with a placebo necessary? Report of patient data from randomized trials of placebo antiemetics with cisplatin. Cancer 1996;78:2193-8.
7. Passalacqua R, Cocconi G, Bella M, et al. Double-blind, randomized trial for the control of delayed emesis in patients receiving cisplatin: comparison of placebo vs. adrenocorticotropic hormone (ACTH). Ann Oncol 1992;3:481-5.
8. Gandara DR, Harvey WH, Monaghan GG, Perez EA, Hesketh PJ. Delayed emesis following high-dose cisplatin: a double-blind randomised comparative trial of ondansetron (GR 38032F) versus placebo. Eur J Cancer 1993;29A:Suppl 1:S35-S38.
9. Kris MG, Gralla RJ, Tyson LB, Clark RA, Cirrincione C, Groshen S. Controlling delayed vomiting: double-blind, randomized trial comparing placebo, dexamethasone alone, and metoclopramide plus dexamethasone in patients receiving cisplatin. J Clin Oncol 1989;7:108-14.
10. Kris MG, Gralla RJ, Clark RA, et al. Incidence, course, and severity of delayed nausea and vomiting following the administration of high-dose cisplatin. J Clin Oncol 1985;3:1379-84.
11. Navari RM, Madajewicz S, Anderson N, et al. Oral ondansetron for the control of cisplatin-induced delayed emesis: a large, multicenter, double-blind, randomized comparative trial of ondansetron versus placebo. J Clin Oncol 1995;13:2408-16.
12. Borison HL, McCarthy LE. Neuropharmacology of chemotherapy-induced emesis. Drugs 1983;25:Suppl 1:8-17.
13. Ireland SJ, Straughan DW, Tyers MB. Influence of 5-hydroxytryptamine uptake on the apparent 5-hydroxytryptamine antagonist potency of metoclopramide in the rat isolated superior cervical ganglion. Br J Pharmacol 1987;90:151-60.
14. Kris MG, Gralla RJ, Tyson LB, et al. Improved control of cisplatin-induced emesis with high-dose metoclopramide and with combinations of metoclopramide, dexamethasone, and diphenhydramine: results of consecutive trials in 255 patients. Cancer 1985;55:527-34.
15. De Mulder PH, Seynaeve C, Vermorken JB, et al. Ondansetron compared with high-dose metoclopramide in prophylaxis of acute and delayed cisplatin-induced nausea and vomiting: a multicenter, randomized, double-blind, crossover study. Ann Intern Med 1990;113:834-40.
16. Kris MG. Phase II trials of ondansetron with high-dose cisplatin. Semin Oncol 1992;19:Suppl 4:23-7.
17. Ruff P, Paska W, Goedhals L, et al. Ondansetron compared with granisetron in the prophylaxis of cisplatin-induced acute emesis: a multicentre double-blind, randomised, parallel-group study. Oncology 1994;51:113-8. [Erratum, Oncology 1994;51:243.]
18. Roila F, Tonato M, Cognetti F, et al. Prevention of cisplatin-induced emesis: a double-blind multicenter randomized crossover study comparing ondansetron and ondansetron plus dexamethasone. J Clin Oncol 1991;9:675-8.
19. Smith DB, Newlands ES, Rustin GJS, et al. Comparison of ondansetron and ondansetron plus dexamethasone as antiemetic prophylaxis during cisplatin-containing chemotherapy. Lancet 1991;338:487-90.
20. Hesketh PJ, Harvey WH, Harker WG, et al. A randomized, double-blind comparison of intravenous ondansetron alone and in combination with intravenous dexamethasone in the prevention of high-dose cisplatin-induced emesis. J Clin Oncol 1994;12:596-600.
21. Roila F, Bracarda S, Tonato M, et al. Ondansetron (GR38032) in the prophylaxis of acute and delayed cisplatin-induced emesis. Clin Oncol (R Coll Radiol) 1990;2:268-72.
22. Hesketh P. Management of cisplatin-induced delayed emesis. Oncology 1996;53:Suppl 1:73-7.
23. Gralla RJ, Rittenberg C, Peralta M, Lertow L, Cronin M. Cisplatin and emesis: aspects of treatment and a new trial for delayed emesis using oral dexamethasone plus ondansetron beginning at 16 hours after cisplatin. Oncology 1996;53:Suppl 1:86-91.
24. Gardner CJ, Bountra C, Bunce KT, et al. Anti-emetic activity of neurokinin NK_1 receptor antagonists is mediated centrally in the ferret. Br J Pharmacol 1994;112:Suppl:516P. abstract.
25. Otsuka M, Yoshioka K. Neurotransmitter functions of mammalian tachykinins. Physiol Rev 1993;73:229-308.
26. Tattersall FD, Rycroft W, Francis B, et al. Tachykinin NK_1 receptor antagonists act centrally to inhibit emesis induced by the chemotherapeutic agent cisplatin in ferrets. Neuropharmacology 1996;35:1121-9.
27. Gardner CJ, Armour DR, Beattie DT, et al. GR205171: a novel antagonist with high affinity for the tachykinin NK_1 receptor, and potent broad-spectrum anti-emetic activity. Regul Pept 1996;65:45-53.
28. Singh L, Field MJ, Hughes J, et al. The tachykinin NK_1 receptor antagonist PD 154075 blocks cisplatin-induced delayed emesis in the ferret. Eur J Pharmacol 1997;321:209-16.
29. Tattersall FD, Rycroft W, Hale JJ, et al. The NK_1 receptor antagonist L-754,030 and its N-phosphoryl prodrug L-758,298 inhibit acute and delayed cisplatin-induced emesis in the ferret. Proc Am Soc Clin Oncol 1998; 17:253a. abstract.
30. Kris MG, Radford JE, Pizzo BA, Inabinet R, Hesketh A, Hesketh PJ. Use of an NK_1 receptor antagonist to prevent delayed emesis after cisplatin. J Natl Cancer Inst 1997;89:817-8.
31. Hesketh PJ, Kris MG, Grunberg SM, et al. Proposal for classifying the acute emetogenicity of cancer chemotherapy. J Clin Oncol 1997;15:103-9.
32. Common toxicity criteria, version 2.0. Bethesda, Md.: National Cancer Institute, March 1998.
33. The Italian Group for Antiemetic Research. Ondansetron + dexamethasone vs metoclopramide + dexamethasone + diphenhydramine in prevention of cisplatin-induced emesis. Lancet 1992;340:96-9.
34. Kris MG, Baltzer L, Pisters KMW, Tyson LB. Enhancing the effectiveness of the specific serotonin antagonists: combined antiemetic therapy with dexamethasone. Cancer 1993;72:Suppl:3436-42.
35. Perez EA. Comparative efficacy of oral and intravenous granisetron for the prevention of acute chemotherapy-induced emesis. Clin Ther 1996;18: 578-90.

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ORIGINAL ARTICLE

Compatibility of intravenous fosaprepitant with intravenous 5-HT_3 antagonists and corticosteroids

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Abstract
Purpose Fosaprepitant dimeglumine for injection is the water-soluble phosphorylated prodrug of the neurokinin-1 receptor antagonist aprepitant. Both agents are approved (in combination with a 5-HT_3 antagonist and a corticosteroid) for prevention of chemotherapy-induced nausea and vomiting. Because fosaprepitant is likely to be combined and stored in the same intravenous (IV) bag with 5-HT_3 antagonists and corticosteroids, the in vitro compatibility of fosaprepitant with these agents and other IV diluents was assessed.
Methods Fosaprepitant (1 mg/mL in 0.9 % sodium chloride injection solution) was combined in binary or tertiary fashion with therapeutic-dose preparations of a 5-HT_3 antagonist (ondansetron, granisetron, palonosetron, or tropisetron) and/or a corticosteroid (dexamethasone sodium phosphate or methylprednisolone sodium succinate). For diluent compatibility assessment, fosaprepitant was also prepared 1 mg/mL in 0.9 % sodium chloride injection solution, water for injection, or 5 % dextrose injection solution. After 24-h storage under ambient conditions, samples were assayed for degradation.
Results Fosaprepitant demonstrated compatibility when combined in the same IV infusion bag with common 5-HT_3 antagonists and corticosteroids for storage and IV coadministration, with the exception of palonosetron (incompatible under all experimental conditions) and tropisetron (incompatible unless combined with a corticosteroid). No incompatibility was observed between fosaprepitant and any of the 3 diluents tested.
Conclusions Use of fosaprepitant in combination with other antiemetics may provide a flexible option for administration of antiemetics to patients receiving moderately or highly emetogenic chemotherapy.

Keywords Fosaprepitant · Emend IV · Corticosteroid compatibility · 5-HT_3 compatibility

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Introduction

Patients receiving chemotherapy for cancer often experience nausea and vomiting, which are distressing adverse events that can be prevented or treated with a variety of antiemetic agents [1]. Effective antiemetics traditionally include selective serotonin-3 (5-HT_3) receptor antagonists, namely ondansetron, granisetron, dolasetron, and tropisetron, as well as the recently approved palonosetron, which offers greater binding affinity for 5-HT_3 and longer half-life compared with the other agents [1]. More recently, understanding the importance of the neurokinin-1 (NK-1) receptor in the emetic pathway has led to the development of a new class of effective antiemetics, the NK-1 receptor antagonists.

Aprepitant, an oral formulation, was the first agent in this class to be approved for the prevention of chemotherapy-induced nausea and vomiting (CINV) [2, 3]. Fosaprepitant dimeglumine for injection (Emend® for Injection, Merck & Co., Inc., Whitehouse Station, NJ) is a water-soluble phosphorylated prodrug of aprepitant that is rapidly dephosphorylated in vivo to the active moiety aprepitant following intravenous (IV) administration.

Fosaprepitant (115-mg free acid equivalent) has been approved as an alternative to the 125-mg oral aprepitant dose given on day 1 of a 3-day regimen, with 80-mg oral aprepitant administered on days 2 and 3 [3, 4]. Subsequently, a 150-mg dose of fosaprepitant has been approved in the EU and USA and is pending approval in other major markets. Although the compatibility study described in this paper was conducted for the 115-mg dose, the results obtained with the 115-mg dose can be extrapolated to the 150-mg dose since both doses have the same formulation composition and are reconstituted to the same final concentration of 1 mg/mL for administration.

A number of large clinical trials have established that addition of an NK-1 receptor antagonist to standard therapy improves the management of CINV in patients receiving highly or moderately emetogenic chemotherapy, with efficacy demonstrated in a broad range of tumor types (e.g., breast, colon, lung, ovarian cancer) [1, 5–9]. In patients receiving highly emetogenic cisplatin regimens, addition of aprepitant to standard antiemetic therapy (ondansetron and dexamethasone) provided improved protection overall (0–120 h postinitiation of chemotherapy) and during both the acute (0–24 h) and delayed phases (25–120 h) of CINV; moreover, aprepitant therapy was generally well tolerated [1, 5, 6, 9]. Similar results have been observed in patients receiving moderately emetogenic regimens [7, 8].

Both aprepitant and fosaprepitant are indicated for use in combination with other antiemetic agents [3, 4]. In patients receiving highly and moderately emetogenic chemotherapy, current guidelines for the treatment of CINV recommend that NK-1 receptor antagonists be used in combination with a 5-HT_3 antagonist and a corticosteroid [10–13]. Review of the available clinical data suggests that the pharmacokinetic interaction of aprepitant with corticosteroids can be managed by dose adjustment of the corticosteroid and that aprepitant has no clinically significant pharmacokinetic interactions with 5-HT_3 antagonists, including palonosetron [14–16].

Decreasing infusion time permits more rapid administration of treatments, allowing more patients to be treated in a given period. For ease of administration and saving of time, fosaprepitant is likely to be combined and stored in the same IV bag with commonly used 5-HT_3 antagonists and corticosteroids. This warrants a thorough understanding of the possible in vitro incompatibilities of fosaprepitant with the other medications. Therefore, two studies were conducted to measure the effects of coadministration of corticosteroids and 5-HT_3 antagonists, as well as those of commonly used IV diluents, on fosaprepitant stability.

Methods

In the first study, fosaprepitant was prepared in the 1-mg/mL concentration used clinically, with the lyophilized contents of one 115-mg vial diluted in 115 mL of 0.9 % sodium chloride injection solution. Corticosteroids and 5-HT_3 antagonist concentrations were equivalent to their recommended therapeutic doses diluted in 115 mL of 0.9 % sodium chloride injection solution. Fosaprepitant solutions were either binary with each 5-HT_3 antagonist or corticosteroid or tertiary with each 5-HT_3 antagonist and each corticosteroid. Tested corticosteroids included dexamethasone sodium phosphate (DSP) and methylprednisolone

Table 1 Compatibility study design: tested combinations and concentrations

Sample	Corticosteroid	Dose (mg)	Diluted concentration (mg/mL)	5-HT_3 antagonist	Dose (mg)	Diluted concentration (mg/mL)
1	None	N/A	N/A	Ondansetron	8.000	0.070
2	None	N/A	N/A	Granisetron	3.000	0.026
3	None	N/A	N/A	Palonosetron	0.250	0.002
4	None	N/A	N/A	Tropisetron	5.000	0.043
5	None	N/A	N/A	None	N/A	N/A
6	DSP	12.000	0.100	Ondansetron	8.000	0.070
7	DSP	12.000	0.100	Granisetron	3.000	0.026
8	DSP	12.000	0.100	Palonosetron	0.250	0.002
9	DSP	12.000	0.100	Tropisetron	5.000	0.043
10	DSP	12.000	0.100	None	N/A	N/A
11	MSS	80.000	0.700	Ondansetron	8.000	0.070
12	MSS	80.000	0.700	Granisetron	3.000	0.026
13	MSS	80.000	0.700	Palonosetron	0.250	0.002
14	MSS	80.000	0.700	Tropisetron	5.000	0.043
15	MSS	80.000	0.700	None	N/A	N/A

DSP Dexamethasone sodium phosphate, *MSS* methylprednisolone sodium succinate, *N/A* not applicable

Table 2 Compatibility results

Sample	Corticosteroid	5-HT_3 antagonist	pH	Change in fosaprepitant (% of label claim)	Increase in degradate (% of label claim)	Particulate analysis	
						Particles ≥10 μm, *n*	Particles ≥25 μm, *n*
1	None	Ondansetron	7.44	−0.3	0.0	584	36
2	None	Granisetron	7.92	−0.3	0.0	362	18
3	None	Palonosetron	6.08	−1.8	1.1	410	34
4	None	Tropisetron	6.83	−1.0	0.2	544	58
5	None	None	8.48	0.3	0.0	866	8
6	DSP	Ondansetron	7.44	−0.1	0.1	314	18
7	DSP	Granisetron	7.66	0.1	0.0	248	10
8	DSP	Palonosetron	6.39	−0.8	0.7	336	16
9	DSP	Tropisetron	7.08	0.0	0.1	288	4
10	DSP	None	8.47	0.4	0.0	304	14
11	MSS	Ondansetron	7.43	−1.0	0.0	508	6
12	MSS	Granisetron	7.50	−0.5	0.0	736	6
13	MSS	Palonosetron	6.89	−0.9	0.3	384	2
14	MSS	Tropisetron	7.30	−0.6	0.1	568	14
15	MSS	None	7.70	−0.9	0.0	1,462	14

DSP Dexamethasone sodium phosphate, *MSS* methylprednisolone sodium succinate, *N/A* not applicable

sodium succinate (MSS). Tested 5-HT_3 antagonists included ondansetron, granisetron, palonosetron, and tropisetron. Specific drug combinations, as well as their concentrations, are shown in Table 1. Each sample solution was stored for 24 h at ambient conditions (approximately 25 °C, 1 atm, ambient humidity and light) to mimic likely clinical conditions. After this period, each sample was assayed by high-performance liquid chromatography (HPLC) for fosaprepitant and fosaprepitant degradate concentrations. Other assessments included particulate matter and the pH of the solution.

Fosaprepitant is incompatible with any solutions containing divalent cations (e.g., Ca^{2+}, Mg^{2+}), such as Ringer's injection and lactated Ringer's injection [4]. Thus, for compatibility testing, fosaprepitant was reconstituted in 0.9 % sodium chloride injection solution, water for injection, and 5 % dextrose injection. Samples were reconstituted with each diluent to a concentration of 1 mg/mL. Fosaprepitant assay and degradate by HPLC, as well as tests for color and clarity, were performed at reconstitution and after 24 h of storage at ambient conditions.

Results

No precipitation was visible in any of the samples after the addition of any steroid/5-HT_3 antagonist combination to fosaprepitant. However, for the purposes of this study, compatibility was defined as (1) a ≤0.2 % increase in degradate level and (2) particulate levels in each container less than the United States Pharmacopeia (USP)—recommended limits for small (100-mL) injection volume (6,000 for particles ≥10 μm; 600 for particles ≥25 μm) [17]. Results of the analyses are shown in Table 2. Based on particle generation, none of the prepared samples failed compatibility. The highest level of particulates was observed in the binary solution of fosaprepitant and MSS (sample 15); nonetheless, it was well below the USP-recommended limits.

Based on the level of degradate formation, several drug combinations appeared unacceptable under experimental conditions. Palonosetron combined with fosaprepitant generated higher than acceptable degradate formation, both in a binary solution and in tertiary solutions, with both tested corticosteroids. Tropisetron was not compatible with fosaprepitant in a binary solution; however, it was compatible when either corticosteroid was added to the solution. The compatibility of each of the steroid/5-HT_3 antagonist drug combinations is summarized in Table 3.

In the study of diluent compatibility, no significant changes were observed in fosaprepitant assay, degradate, color, or clarity in 0.9 % sodium chloride injection solution, water for injection, or 5 % dextrose injection (Table 4). Results were similar after reconstitution and after 24 h of storage at ambient conditions, with a maximum 0.1 % of degradate formation in all 3 diluents over 24-h storage with minimal change for the fosaprepitant assay.

Table 3 Compatibility of fosaprepitant with steroid/5-HT_3 combinations

Corticosteroid	5-HT_3 antagonist	Compatibility with fosaprepitant
None	Ondansetron	+
None	Granisetron	+
None	Palonosetron[a]	–
None	Tropisetron[b]	–
DSP	Ondansetron	+
DSP	Granisetron	+
DSP	Palonosetron	–
DSP	Tropisetron	+
MSS	Ondansetron	+
MSS	Granisetron	+
MSS	Palonosetron	–
MSS	Tropisetron	+

+, compatible; –, incompatible; DSP, dexamethasone sodium phosphate; MSS, methylprednisolone sodium succinate

[a] Palonosetron can be administered over 30 s in clinical practice; thus, there is no advantage to putting palonosetron in the same infusion bag with fosaprepitant

[b] Tropisetron can be coadministered with fosaprepitant using a Y line (or directly into the vein), with no likely negative effects

Discussion

The present studies evaluated in vitro the effects of concomitant dilution and storage of fosaprepitant IV with corticosteroids and 5-HT_3 antagonists. Fosaprepitant was compatible with most combinations; however, fosaprepitant was incompatible with palonosetron in any combination under the experimental conditions and with tropisetron unless a corticosteroid was added to the solution.

The incompatibility of fosaprepitant with palonosetron was characterized by unacceptable levels of fosaprepitant degradation. Incompatibility was correlated with relatively low pH values, suggesting that fosaprepitant degradation may be a result of the reduction in pH associated with the addition of palonosetron. A similar result was observed with the addition of tropisetron; however, the incompatibility was absent upon the addition of either corticosteroid. In this case, the addition of corticosteroid formulations likely prevented a significant increase in fosaprepitant degradate by adding to the buffering capacity of the solution.

Incompatibility due to a pH discrepancy has been recognized for decades; however, precipitate-induced incompatibility cannot be predicted from pH alone; the presence of additives, storage temperatures, or the method of administration may also result in precipitation [18, 19]. Thus, it is vital to test putative drug combinations under typical clinical conditions to establish the feasibility of coadministration. Despite the seeming incompatibility of fosaprepitant with palonosetron under experimental conditions, the drugs can be coadministered in accordance with instructions in the palonosetron prescribing information [20]. Because palonosetron is administered IV over 30 s, rather than remaining in solution for 24 h, it would be in contact with fosaprepitant for ≲30 s, thereby minimizing the decrease in pH and the subsequent kinetic degradation of fosaprepitant. Although IV push medications are broadly defined as those that can be administered in <15 min, palonosetron can be administered over 30 s in clinical practice; thus, there is no time or administration advantage to putting palonosetron in the same infusion bag with fosaprepitant or other antiemetics. Similarly, for ease of administration and saving of time, tropisetron can be coadministered with fosaprepitant using a Y line (or directly into the vein), likely with no negative effects. However, if an infusion or drip bag is used, it is not recommended that tropisetron be combined with fosaprepitant in the absence of DSP or MSS.

A limitation of this study was the lack of testing of the coadministration effects on the corticosteroids and 5-HT_3

Table 4 Diluent compatibility results

	Fosaprepitant and degradate changes					
	Fosaprepitant			Degradate		
Diluent	Initial (% of label claim)	24 h (% of label claim)	Change in % of label claim	Initial (% of label claim)	24 h (% of label claim)	Change in % of label claim
0.9 % sodium chloride injection	95.3	96.0	0.7	0.2	0.3	0.1
	97.2	98.1	0.9	0.3	0.3	0.0
	98.1	98.4	0.3	0.2	0.3	0.1
	97.7	98.0	0.3	0.3	0.3	0.0
	96.8	96.7	−0.1	0.3	0.3	0.0
Water for injection	98.0	98.6	0.6	0.3	0.3	0.0
	97.2	97.5	0.3	0.3	0.3	0.0
	97.2	97.5	0.3	0.3	0.3	0.0
5 % dextrose injection	97.7	98.3	0.6	0.2	0.3	0.1

antagonists due to limited access to relevant analytical methods, reference standards, and associated specifications for these marketed products. Thus, although no negative effects were observed on fosaprepitant in combinations deemed compatible, the effects of the combination on the other solution components are unknown.

Conclusions

The addition of NK-1 receptor antagonists to standard therapy has improved the management of CINV in patients receiving highly or moderately emetogenic chemotherapy, thereby addressing a major unmet need in CINV patients by improving chemotherapy compliance and quality of life [5–8].

Fosaprepitant, in combination with other antiemetics, is likely to be used to provide such care, necessitating the investigation of drug–drug interactions. In addition to previous reports of minimal pharmacokinetic interaction with other antiemetics, compatibility of fosaprepitant has now been demonstrated when combined in the same IV infusion bag with common 5-HT_3 antagonists and corticosteroids for storage and IV coadministration. Furthermore, fosaprepitant is compatible for reconstitution in 0.9 % sodium chloride injection solution, water for injection, or 5 % dextrose injection. These data support the ability to use fosaprepitant in combination with other antiemetics to provide a flexible option for administration of antiemetics to patients receiving moderately or highly emetogenic chemotherapy.

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Conflict of interest The original studies were supported by Merck Sharp & Dohme Corp., Whitehouse Station, NJ, USA. S. Sun, J. Schaller, J. Placek, and B. Duersch are employees of Merck and may own stock/stock options in the company.

References

1. Hesketh PJ (2008) Chemotherapy-induced nausea and vomiting. N Engl J Med 358:2482–2494
2. Aapro MS, Walko CM (2010) Aprepitant: drug–drug interactions in perspective. Ann Oncol 12:2316–2323
3. Emend (aprepitant) capsules [package insert]. Whitehouse Station, NJ: Merck & Co., Inc., 2003
4. Emend (fosaprepitant dimeglumine for injection) [package insert]. Whitehouse Station, NJ: Merck & Co., Inc., 2008
5. Hesketh PJ, Grunberg SM, Gralla RJ et al (2003) The oral neurokinin-1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting: a multinational, randomized, double-blind, placebo-controlled trial in patients receiving high-dose cisplatin—the Aprepitant Protocol 052 Study Group. J Clin Oncol 21:4112–4119
6. Poli-Bigelli S, Rodrigues-Pereira J, Carides AD et al (2003) Addition of the neurokinin 1 receptor antagonist aprepitant to standard antiemetic therapy improves control of chemotherapy-induced nausea and vomiting. Results from a randomized, double-blind, placebo-controlled trial in Latin America. Cancer 97:3090–3098
7. Warr DG, Hesketh PJ, Gralla RJ et al (2005) Efficacy and tolerability of aprepitant for the prevention of chemotherapy-induced nausea and vomiting in patients with breast cancer after moderately emetogenic chemotherapy. J Clin Oncol 23:2822–2830
8. Rapoport BL, Jordan K, Boice JA et al (2010) Aprepitant for the prevention of chemotherapy-induced nausea and vomiting associated with a broad range of moderately emetogenic chemotherapies and tumor types: a randomized, double-blind study. Support Care Cancer 18:423–431
9. Schmoll HJ, Aapro MS, Poli-Bigelli S et al (2006) Comparison of an aprepitant regimen with a multiple-day ondansetron regimen, both with dexamethasone, for antiemetic efficacy in high-dose cisplatin treatment. Ann Oncol 17:1000–1006
10. Jordan K, Sippel C, Schmoll HJ (2007) Guidelines for antiemetic treatment of chemotherapy-induced nausea and vomiting: past, present, and future recommendations. Oncologist 12:1143–1150
11. Herrstedt J (2008) Antiemetics: an update and the MASCC guidelines applied in clinical practice. Nat Clin Pract Oncol 5:32–43
12. Herrstedt J, Roila F (2008) Chemotherapy-induced nausea and vomiting: ESMO clinical recommendations for prophylaxis. Ann Oncol 19 (Suppl 2):ii110–ii112
13. Kris MG, Hesketh PJ, Somerfield MR et al (2006) American society of clinical oncology guideline for antiemetics in oncology: update. J Clin Oncol 24:2932–2947
14. Blum RA, Majumdar A, McCrea J et al (2003) Effects of aprepitant on the pharmacokinetics of ondansetron and granisetron in healthy subjects. Clin Ther 25:1407–1419
15. Shah AK, Hunt TL, Gallagher SC, Cullen MT Jr (2005) Pharmacokinetics of palonosetron in combination with aprepitant in healthy volunteers. Curr Med Res Opin 21:595–601
16. McCrea JB, Majumdar AK, Goldberg MR et al (2003) Effects of the neurokinin1 receptor antagonist aprepitant on the pharmacokinetics of dexamethasone and methylprednisolone. Clin Pharmacol Ther 74:17–24
17. Convention United States Pharmacopeial (2009) Particulate matter in injections. USP NF 2010. U.S. Pharmacopeia, Rockville
18. Eisenberg S (1997) Intravenous drug compatibility: a challenge for the oncology nurse. Oncol Nurs Forum 24:859–869
19. Longfield V (2003) Compatibility and stability of 5-HT3 receptor antagonists: a pharmacology review. Oncol Nurs Forum 29:1469–1482
20. Aloxi (palonosetron HCl) [package insert]. Helsinn Healthcare: SA Switzerland, 2009

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処方的乳化と機械的乳化のバランスを考えた乳化技術

高木 和行

Abstract : Various emulsification technology has been developed. Regarding formulation emulsification technology, the phase inversion emulsifying method, the gel emulsifying method, and the D phase emulsifying method are used. As a form of mechanical emulsification technology, there is also the emulsifying method in which mechanical power (mainly shear, impact, cavitation) is applied. Use of mechanical emulsification as the manufacturing technology helps in such a formulation. The search for a harmonization of formulation, materials, manufacturing process, and production equipment for new product development is increasingly important.

Key words : harmonization, formulation and mechanical emulsification emthod

1．はじめに

化粧品には基礎化粧品を中心に乳化製品が多く，多種類の処方的乳化方法が考案され利用されてきた。また，乳化装置も多種多様な装置が開発され使用されている。

従来は，処方的な乳化と機械的な乳化に分けて考えられてきたが，近年，両者のバランスを取ることの重要性がクローズアップされている。また，機械的な力を利用して素材の特性を生かした製造技術も重要になってきている。

2．処方的乳化と機械的乳化

処方的乳化は，界面科学的特性を利用する方法で，ファクターとして，界面張力，静電気的斥力・引力，比重・密度などがある。機械的乳化とは，機械力を使用し乳化微粒子を得る方法である。化粧品業界では，乳化剤を少なくする要望が強く，処方的乳化と機械的乳化のバランスを考えることが重要となっている。また，処方に適した撹拌羽根形状が選定されるようになっている。処方的乳化方法として，石鹸乳化法，反転乳化法，転相温度乳化法（PIT温度乳化法），ゲル乳化法やD相（界面活性剤相）乳化法などがある。その他に，乳化特性をもった原料を利用する乳化方法があり，粘土鉱物，レシチン，タンパク質などが使用されている。この場合，求められるエマルジョンに応じて最適な装置を選定することが非常に重要である。

2-1．安定な乳化製品を製造する方法

乳化物は熱力学的には不安定で，いつかは分離するものである。その安定性が良いほど，良い乳化と言われる。エマルジョンを安定にする因子はいくつかあるが，粒子を均一に小さくすることが重要である。

分散相の分裂によるエマルジョン粒子の発生は，分散系に付加される機械的エネルギーレベルによる分裂作用（Ed）と，液-液分散系の物性に

"New emulsification technology searching for a harmonization of formulation and mechanical emulsification method."
Kazuyuki Takagi (Mizuho Industrial Co., Ltd., みづほ工業株式会社技術担当取締役 〒557-0063 大阪市西成区南津守4-4-16)



1956年生まれ，大阪市出身。1982年岡山大学大学院化学工学修士課程修了，同年みづほ工業入社，1996年岡山大学にて工学博士号取得，現在同社常務取締役。

Page 566 of 596

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起因する分裂抵抗（界面張力による分裂抵抗（Es）と分散相粘度による分裂抵抗（Ev））とのバランスにより決まる[1]。この時の平均粒子径：dpは，撹拌速度：Nr，羽根径：dl，界面張力（処方的な要素）：γ，分散相および連続相の粘度：μd，μc，分散相および連続相の密度：ρd，ρcにより表される。

①界面張力支配（Ed＝Es）

$$dp/di = C_1(\rho c \cdot Nr^2 \cdot di^3/\gamma)^{-0.6} \quad \text{式－1}$$

②粘性力と界面張力の合成力支配

$$\rho c \cdot Nr^3 \cdot di^{7/3} \cdot dp^{5/3}/\gamma = C_2[1 + C_3(\rho c/\rho d)^{1/2} \cdot \mu d \cdot Nr \cdot di^{2/3} \cdot dp^{7/3}/\gamma] \quad \text{式－2}$$

③粘性力支配

$$dp/di = C_3(\rho c/\rho d)^{3/4} \cdot (\mu d/\mu c)^{1/4} \cdot (\rho c \cdot Nr \cdot di^2/\mu c)^{-1/4} \quad \text{式－3}$$

以上のことから，目的とする粒子径は，処方的な力と機械力のバランスによって決まるといえる。また，近年，乳化剤を減少させる要望が強いため，乳化微粒子を得るには，機械的な乳化に依存する部分が多くなっていることも説明できる。

2-2. 処方的乳化方法と最適な撹拌羽根

乳化製品の多くは，真空乳化装置（図１）で製造されている。その乳化装置も多くの撹拌羽根形状がある。従来は，高速高せん断ミキサーであるホモミキサーと掻取ミキサーを装備したVQ型または，パドルミキサーも装備したVT型（図２）がほぼ標準的に使用されてきた。近年，製品の差別化のため，処方と製造プロセスが複雑化している。そのため，乳化プロセスに最適な撹拌羽根を選定することが重要となってきている。

①右巻乳化法

脂肪酸（油相）とアルカリ（水相）の中和反応で乳化剤を作り，乳化する方法。一般的に，ホモミキサーなどの大きな機械力は不要である。図３のVS型または，VP型の羽根形状でよい。しかし，最近の非イオン乳化剤との混合系ではホモミキサーを使用するケースもある。その場合，図２の形状が必要となる。

②反転乳化法

油相と水相の容積分率によって，外相と内相を反転させて乳化する方法。近年，ホモミキサーを必要とする処方が多いので，VQ・VT型（図２）が使用されている。

③転相温度乳化法（HLB一温度乳化法）

転相温度付近でエマルジョンが，油相（O），界面活性剤相（D），水相（W）の３相に分離し，この３相領域が現れる温度域で界面張力が最低となることを利用して，小さな乳化粒子を得る乳化方法。近年，ホモミキサーを必要とする処方が多

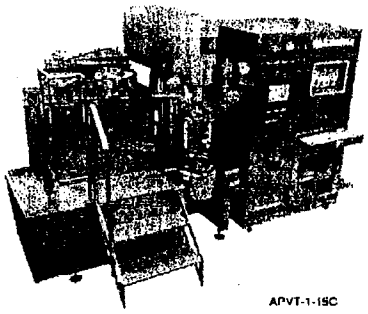


図１　真空乳化装置

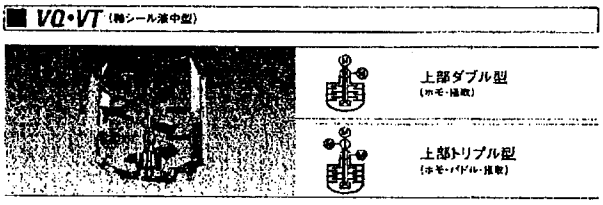


図２　VQ・VT型

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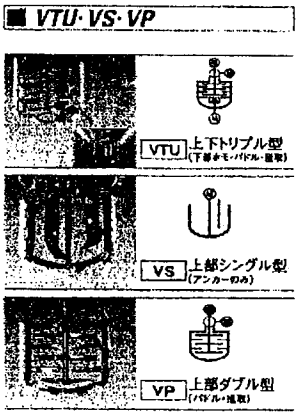


図３　VTU・VS・VP型

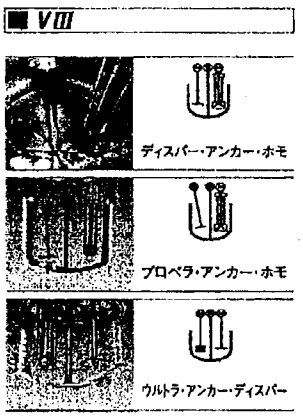


図４　VIII型

いので，VQ・VT型（図２）が使用されている。

④ゲル乳化法

アミノ酸水溶液に，攪拌しながら乳化剤を添加して，ラメラ液晶中に水相が分散したゲルを調整し，そのゲルを油相に分散させる。次に，水相を添加しながら乳化を行う方法。W/Oエマルジョンの調製法である。一般的に，ホモミキサーを必要とする，図４のVIII型の羽根形状がよい。

⑤D相乳化法（界面活性剤相乳化法）

乳化剤と多価アルコールにオイルを添加してD相を調整し，D相に水を添加して小さなO/W乳化粒子を得る方法。多価アルコールとしてポリオールなどを使用する。機械力を使用しないで，少量の乳化剤でファインな乳化ができるのが特徴である。装置としては，オイルの滴下時に掻取ミキサーに付着するのを防ぐため，図３のVS型が便利である。しかし，最近の初期に水相を加える処方では，ホモミキサーやディスパーミキサーを装備した図４のVIII型が使用される。

⑥高分子原料を使用する乳化

高分子原料は，カーボポール，カラギンナン，カルボキシメチルセルロースなど，多くのものがある。従来，乳化安定助剤としての使用が多かったが，高分子原料の界面機能の見直しによって，利用範囲が増大している。その長所としては，HLBの検討が不要であることや乳化粒子が大きくても安定にできることがあげられる。今後，異なる電荷を持った高分子原料の組み合わせを検討することが重要なポイントとなっている。この場合，高分子の分散プロセスによって色々な攪拌羽根形状が使用されている。

⑦粘土鉱物を使用する乳化

Na型モンモリロナイトの層状構造の層間に水を取り込む性質を利用する方法。特徴としては，使用性の軽い乳化物の調整が可能，多様の多価アルコールの使用が可能，温度依存性のない製品ができるなどがある。他に，有機変性粘土鉱物とノニオン性界面活性剤を組み合わせることも多く行われている。また，第４級アンモニウム型有機カチオンとカチオン交換したものは疎水性となり，層状構造間に油を取り込みO/W型エマルジョンを調製することができる。機械力としては，高圧ホモジナイザー（図５）が多く使用されている。

⑧レシチンを使用する乳化

水に分散し難い水素添加レシチンを使用する場合と，分散しやすい水酸化レシチンなどを使用する場合によって乳化装置が異なる。一般的に，水素添加レシチンを使用する処方では，高圧ホモジ

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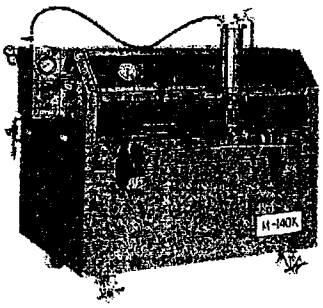


図5　高圧ホモジナイザー(マイクロフルイダイザー)

ナイザー（図5）や超高速高せん断ミキサーが使用される。

⑨シリコーン系乳化剤を使用する乳化

さっぱりした使用感をもったW/O型エマルジョンを調製するためにシリコーンを使用し，それらを乳化するために親油性のポリエーテル変性シリコーンを乳化剤として使用する。洗浄性を優先することが多く，ディスパーミキサーを装備した形状が使用される。

⑩多重エマルジョンを調整する乳化

一般的には二段乳化法によって調整されるが，膜乳化法によって均一な粒子径の多重エマルジョンを調整することも検討されている。二段乳化法の場合，まず高濃度親油性乳化剤を使用してW/O型エマルジョンを調整し，次に低濃度親水性乳化剤を使用してW/O/W型エマルジョンを調製する。一段目では，ホモミキサーやマイクロフルイダイザーが多く使用されている。

2-3. 乳化に有効な機械力

乳化に有効な機械力には，せん断力，衝撃力，キャビテーション力がある。この機械力の中で，一番乳化に効果的に働くのはせん断力であり，近年，強力なせん断力が必要とされている。せん断力とは，図6に示すように，2枚の板の間に試料をセットし，1枚の板を移動させた時に試料を引きちぎる力のことで，2枚の板のクリアランスが狭い程，また，移動する板の速度が大きいほど大きくなる。乳化物では，チクソ性を示すものが多



図6　せん断力

く，その場合，2枚の板の間に生じる速度勾配が直線とならないで，移動する板の近くで，急激に大きくなる。そのため，クリアランスが狭いことが重要である。なぜならば，クリアランスが大きいとせん断力をほとんど受けないで，せん断を受ける場を通過してしまうことになる。乳化物の安定性には，粒度分布も重要で，大きい粒子と小さな粒子があると，小さな粒子が大きな粒子に取り込まれるため，安定性が悪くなる。そのため，乳化物の製造装置には，ホモミキサーやウルトラミキサーのような，局所せん断ミキサーが使用されるケースが多い。ただし，化学品の乳化重合などの場合，せん断力が強すぎると乳化が破壊され凝集物が増えるが，弱すぎると乳化が不十分となり凝集物が増えるため，槽内全体に均一なせん断力を与えることができる大型翼（図7）が多く採用されている。

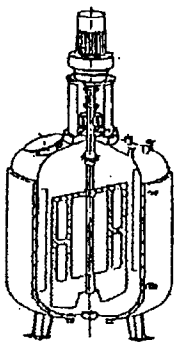


図7　大型翼（マックスブレンド）

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2-4. 乳化に使用できる撹拌羽根および乳化装置

2-4-1. 低速撹拌機

通常の撹拌装置で，一般に回転速度は緩やかである。

①アンカー型（図３：VS型）

高粘度製品製造の場合でも，槽内全体の混合・撹拌ができる。冷却工程で，油相成分が凝固して増粘する乳化物の製造には，槽内壁の伝熱境膜を掻き取るためにテフロン製のスクンバー（図８）を装備した掻取ミキサーが使用される。石鹸乳化法，反転乳化法や転相温度乳化法のように，高せん断力が必要のない乳化や，ゲル乳化法やD相乳化法などのように撹拌しながら後から原料を徐々に添加する工程のある乳化法に適している。

②パドル型

プロペラミキサーよりは高い粘度の液体にも使用できる。図３にパドルミキサーと掻取ミキサーの組み合わせた型（VP型）を示す。

③プラネタリーミキサー

２枚の羽根（図９）がプラネタリー（遊星）運動することによって混練を行う。超高粘度製品や粉体の練合や混合に，また，超高粘度乳化製品の粒子径を揃えるためにも使用する。羽根間のクリアランスが狭い形状や，撹拌羽根と同じように回転する温度センサー，高速高剪断ミキサーも装備したネリマゼ型（図10）などの開発により，使用範囲が増大した。ニーダーのように，液中に軸シールが存在しないのでサニタリー性や洗浄性に優れる。また，冷却途中で大きく増粘し，パールの結晶がでてくる洗顔石鹸や，ドロパックなどのパック類の製造には，複合的なネリマゼ型が多く使用されるようになっている。

2-4-2. 高速高せん断ミキサー

①ホモミキサー（図11）

高速回転するタービン羽根とステーターの間に生じる強力なせん断力，衝撃力，キャビテーションによって乳化を行う。ステーター内のタービン羽根を高速回転させることにより，タービン羽根の上部と底部の間にキャビテーションを生じさせ，ポンプのような働きを起こし，絶えず流体を底部から吸い上げる。ステーターとタービン羽根の隙間は約0.5mmで，流体はこの隙間を通過し



図８　テフロン製スクレパー

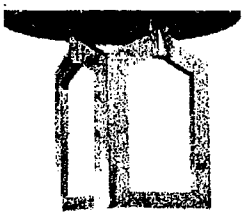


図９　プラネタリーミキサー



図10　複合的な撹拌羽根



図11　ホモミキサー

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て上部に押し出される。その時に強力なせん断力を受ける。一般的に低粘度型と高粘度型がある。低粘度型は，約７Pasの粘度の製品まで使用できるが，約４Pasの粘度より吐出量が減少するため，それ以上の粘度の場合には，高粘度型を使用する場合が多い。

②ディスパーミキサー（図12）

粉体を液体に分散させるサスペンション系に適している。高分子増粘剤を効率良く分散させるために使用される。乳化にも多く使用されているが，スケールアップに注意が必要である。邪魔板を設けて生ずる渦を壊すと上下対流が生じて撹拌効果も増大する。

③ウルトラミキサー（図13）

上から自重で降りてくる製品を，キャビテーションによる吸引力と回転フードによる掻き込みによってミキサー内に吸い込み，側面より吹き出す。上の回転側が３重，下の固定側が２重のスリットになっているため，この間を通過する製品にホモミキサーの約３～５倍の強力なせん断力を与えることができる。高粘度製品に高せん断力を与えることができるミキサーである。約100Pas（10万c.p.s.）の高粘度にまで使用できる。上部ウルトラミキサーも多く使用されている。



図12　ディスパーミキサー

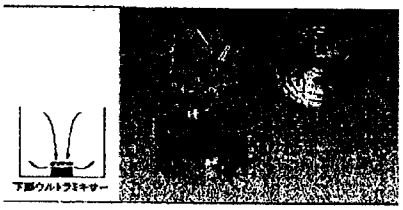


図13　ウルトラミキサー

近年，ホモミキサー以上に高剪断力をもち，高粘度製品に対しても効果を発揮する撹拌機の需要が増加している。ホモミキサーやディスパーミキサーを超高速回転仕様（生産機でMax. 10,000rpm）に改良して対応する場合もあるが，ウルトラミキサーの使用が増加している。高分子溶液のレオロジー特性を小さくして，品質管理を楽にすることにも利用されている。

2-4-3. 高圧ホモジナイザー（マイクロフルイダイザー：流路固定式高圧ホモジナイザー：図５）

チャンバー内で原料の流れを二手に分け（図14），275Mpaの超高圧で細管内を通過させ，その時に強力なせん断力を与える。その後，原料の流れを再び合流させ，衝突させて衝撃力を与える。超高圧下で処理するため，他の装置で分散しなかった原料にも効果を発揮し，0.5μm以下の微細エマルジョンの製造もできる。高圧ホモジナイザーにおける粒子径の制御は、処理圧力に大きく依存する。しかし乳化粒子が小さいとブラウン運動によって衝突の機会が増えるので，組成をよく検討して安定なエマルジョンとしなければならない。ホモミキサーで５μmの粒子径になるものと同じ処方で，マイクロフルイダイザーを使用すると0.1μmの微粒子が得られることと，ほぼ同じ５μmの粒子径では，乳化剤量をホモミキサーの４％から0.18％まで減少させることもできる。

乳化剤フリーの化粧品クリーム製造や細胞破砕，細胞破砕を利用した防腐剤フリーの化粧品製造にも使用されている。

高分子を含んだ処方に使用する場合には，分子鎖切断や構造破壊の有無を確認する必要がある。

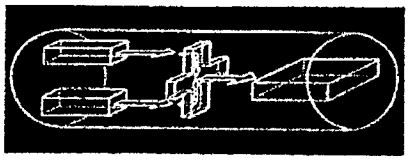


図14　マイクロフルイダイザーのチャンバー図

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2-4-4. 超音波乳化装置

液体に強力な超音波を加えると過圧と負圧が発生し，負圧によって液体が引裂かれることによって空洞が生じる，その空洞が潰れる時に衝撃波が発生する。このキャビテーション力によって局所的な乳化を行う。超音波を発生するシステムには，機械的振動方式と電気的振動方式がある。振動数によっては，乳化破壊を起こす場合もあり，処方と振動数のマッチングが大切である。レチンの分散に使用されているケースがある。エマルジョンに及ぼす超音波波長の影響などの研究が進んでいる[7]。

最近では，200Khの超音波洗浄器や数種類の波長を発振できる装置も販売されている。

2-4-5. 膜乳化装置（図15）

多孔質膜をある条件で通過した液は一定の粒子径をもつという現象を利用し，微粒子から大粒子の均一な粒子径をもったエマルジョンを作ることができる。また多重乳化も可能である。膜の表面の性質によってW/O型でもO/W型でも調製できることも特長である。しかし，膜が弱いことや洗浄性が悪いこと，生産性の問題などがあり，下備乳化を行った後膜を通過させる方法[8]や膜の選定など，改良や研究が行われている。

3．製品の冷却

多くの乳化製品の製造には冷却プロセスがある。近年，処方の複雑化から，冷却プロセスの制御が乳化製品の品質に大きく影響するケースが増加している。特にスケールアップにおいて問題となることが多い。

エマルジョン中の油脂結晶が成長して粗大化すると界面を破り，部分的な合一を引き起こすことが報告されている[9]。

乳化装置としては，伝熱不良を解消し，冷却効率をアップするために，テフロン製スクレパー（図８）付き掻取ミキサーを採用している。従来はスクレパーをほとんど採用されなかった化学品業界でも，樹脂の乳化で多く採用されるようになっている。

常温で固体のワックスを乳化した後の冷却工程では，温度境界層が生じ，これを掻き取る必要が

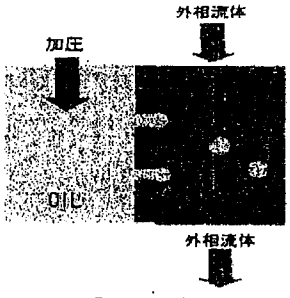


図15　膜乳化

出てくる。特に，高粘度製品では伝熱面の温度境界層が厚くなる。この境界層の影響を少なくすることによって，伝熱不良を解消し，冷却効率をアップすることができる。ただし，スクレパーによって槽内壁に生じる温度境界層を掻取ることができるが，底面を掻取れないコイルなどの使用は難しくなり，そのような処方に対しては，ジャケット面からの伝熱に限られることになる。そうすると，単位体積当たりの伝熱面積が大きくできないので，伝熱（加熱・冷却）に要する時間が長くなる。

ジャケット方式による冷却時間は次式（Bach Cooling式）により求まる。

$$\ln(T_1 - t_1/T_2 - t_1) = (\omega C_2/MC_1) \cdot (K_3 - 1/K_3) \cdot \theta \quad \text{式－4}$$

$K_3 = \exp(UA/\omega C_2)$

T_1：製品の冷却開始温度［K］

T_2：製品の冷却終了温度［K］

t_1：冷却水温度［K］

ω：冷却水量［Kg/hr］

C_1：製品の比熱［J/Kg·K］

C_2：冷却水の比熱［J/Kg·K］

M：製品の仕込量［Kg］

θ：冷却時間［hr］

U：総括伝熱係数［W/m²·K］

A：伝熱面積（ジャケット面積）［m²］

ただし，スケールアップの比率が大きい場合，冷却時間の増加により製品物性に変化が生じることがあるので，注意が必要である。特に，同じ粘度にならないケースがある。そのような場合には，

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周速度を一定にしたスケールアップから，単位体積あたりのエネルギー量を一定にしたスケールアップの考え方に変更した方が良いケースがある。

$$W = Kw \cdot T/V \qquad 式－5$$

W　：エネルギー量［J］
Kw：動力［W］
T　：冷却時間［hr］
V　：製品の仕込量［Kg］

スクレパーを装備することの欠点として，洗浄性が悪くなることがあげられるが，掻取ミキサーの正逆転用スクレパーを採用することにより解消できる。

また，温度センサーの選定および取付け方法も重要である。通常は，槽底付近から棒状の温度センサーを突出させるタイプが多いが，槽底における温度センサーの取付け円周上がスクレパーで掻取ることができなくなる。その掻き取れない部分に乳化物が固化してトラブルを発生するケースがある。この場合，膜式の温度センサーを採用するケースもある。しかし，膜式の温度センサーでは，高粘度製品の温度境界層の温度しか測定できない問題が発生する。それに対して，温度センサーが槽内で移動する仕様（図10）が有効となる。

4．有機溶剤フリーの乳化

化学品業界では，塗料や接着剤の分野において，乳化技術が重要な役割を果たしている。従来の有機溶剤への単純な溶解タイプでなく，近年VOC（Volatile Organic Compound）への対応から有機溶剤を使用しない，乳化タイプの製品が増加している。例えば，乳化系接着剤の製造において，転相時に高せん断力が必要となるため，ウルトラミキサーとディスパーミキサーを装備したタイプが採用されることが多い（図4）。また，樹脂の乳化を転相乳化法で行う場合，転相点近くから水相原料の添加に伴って非常に高粘度となる。そのときに，水相原料の添加後少しの時間，添加を止めて，水相原料が全体にいきわたるのを待つ工程がある。この場合，撹拌動力を非常に強大なものにして，水相原料の連続投入の可能性もあるが，転相後が非常に低粘度になることもあり，経済的に考えて，製造プロセスの操作での対応によって撹拌動力を押さえるケースが多い。

強制乳化法に分類される溶媒ポリマー乳化法やポリマー溶融乳化法では，ホモミキサーや高圧ホモジナイザーも利用されている。

塗料の分野では，水分散性ポリマーの分散も重要なプロセスで，それに対応した撹拌羽根も必要となる。特殊な塗料には，高圧ホモジナイザーも使用されている。また，乾燥スピードを速くする目的や塗膜の強度を高めるために，乳化剤を減少させる要望も増加している。

化粧品では，ネイル製品において，アセトンフリーの需要が増え，乳化技術に依存する製品が増加している。

5．ナノエマルジョン

医薬品業界では，レシチンを使用して大豆油などを乳化し，50nm超微粒子である脂肪乳剤の製造が行なわれている。これは，LNS製剤という注射剤である。この製造には，マイクロフルイダイザーが使用されている。一方，機械力を使用しないで，高分子のミセルを利用した，ナノメディシンの開発も行なわれている。

化粧品業界でもナノエマルジョンやリポソームの要望が多い。

6．おわりに

今後，ユーザーにおける新製品の開発方法として，処方的な力と機械的な力のバランスを考えた製造技術の開発が大きな流れのひとつになるものと予想される。また，処方，原料，製造プロセス，製造設備の調和点を求めることの重要性も増大している。このため，製造設備に要求される内容も複雑かつ多様化してきている。

参考文献

1）田中眞人，田口佳成，化学工学，67(11)，625～628（2003）
2）マックスブレンド，住友重機械工業㈱
3）酒井秀樹，第49回界面科学部会秋季セミナーテキスト（日本油化学会界面科学部会）（2002）
4）鈴木寛一，羽倉義雄，*Japan J.Food. Engineering*，3(2)，35（2002）
5）佐藤清隆，オレオサイエンス，5(1)，3（2005）

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ORIGINAL ARTICLE

Pharmacokinetics of aprepitant and dexamethasone after administration of chemotherapeutic agents and effects of plasma substance P concentration on chemotherapy-induced nausea and vomiting in Japanese cancer patients

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Abstract
Purpose This study was conducted to determine the pharmacokinetics of aprepitant and dexamethasone as well as the relationship between the plasma concentration of substance P and nausea/vomiting in Japanese cancer patients.
Methods After administration of aprepitant (125/80 mg group [10 patients]: 125 mg on day 1 and 80 mg on days 2–5; 40/25 mg group [10 patients]: 40 mg on day 1 and 25 mg on days 2–5) and dexamethasone (6 mg on day 1 and 4 mg on days 2 and 3 in the 125/80 mg group, and 8 mg on day 1 and 6 mg on days 2 and 3 in the 40/25 mg group) to Japanese cancer patients receiving at least moderately emetogenic antitumor agents, the plasma concentrations of aprepitant, dexamethasone, and substance P were measured.
Results All of 20 patients were treated with the highly emetogenic agent cisplatin (≥70 mg/m^2). The C_{max} and $AUC_{0-24\ h}$ of aprepitant in Japanese cancer patients were similar with those in non-Japanese patients. The clearance of dexamethasone in the 125/80 mg group was approximately one-half of that previously determined in the absence of aprepitant. The substance P concentration in plasma significantly increased only in patients with delayed nausea/vomiting.
Conclusions This study demonstrated similar plasma pharmacokinetics of aprepitant in Japanese and non-Japanese, the validity of reducing dexamethasone dose, and the existence of increased plasma substance P concentration in patients receiving highly emetogenic cisplatin-based chemotherapy.

Keywords Aprepitant · Dexamethasone · Substance P · Pharmacokinetics · Chemotherapy-induced nausea and vomiting

Introduction

Aprepitant is a neurokinin-1 (NK_1) receptor antagonist developed as a treatment for both acute and delayed chemotherapy-induced nausea and vomiting (CINV). It has a novel mechanism of action (i.e., by inhibiting the binding of substance P to the NK_1 receptor in the vomiting center) [1–3]. In the guidelines for management of CINV, aprepitant is recommended to be used in combination with a serotonin antagonist and dexamethasone to prevent nausea/vomiting induced by highly and moderately emetogenic cancer chemotherapy [4–6].

Although aprepitant has no effect on the pharmacokinetics of serotonin antagonists (ondansetron, granisetron, palonosetron) [7, 8], aprepitant inhibits CYP3A4 and in turn inhibits the metabolism of dexamethasone, a substrate of CYP3A4 [9]. It has been shown that the area under the concentration–time curve (AUC) of dexamethasone is increased approximately two times after administration of aprepitant at a dose of 125 mg on day 1 and at a dose of 80 mg on days 2–5 in healthy adults, and so, to maintain

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dexamethasone at the prescribed blood level in the presence of aprepitant, the dose of dexamethasone has to be reduced by 50% [9]. Although a previous population pharmacokinetic study of dexamethasone combined with aprepitant supported the validity of this dose reduction of dexamethasone [10], there has been no full pharmacokinetic study of dexamethasone and aprepitant in cancer patients who receive emetogenic cancer chemotherapy.

While aprepitant may have an antiemetic effect by inhibiting the binding of substance P to the NK_1 receptor in the vomiting center as mentioned above, it is still unclear whether there is any change in the in vivo kinetics of substance P after administration of chemotherapeutic agents, or how the in vivo kinetics of substance P is related to CINV.

This study was conducted to determine the pharmacokinetics of aprepitant as well as dexamethasone in Japanese cancer patients and to verify the dose reduction of dexamethasone used in combination with aprepitant, and furthermore, to evaluate the relationship between CINV and in vivo kinetics of substance P after administration of chemotherapeutic agents.

Patients and methods

Inclusion criteria

Japanese cancer patients aged between 20 and 74 years who received cancer chemotherapy were included in this study. Cancer chemotherapy consisted of at least moderately (Hesketh level ≥ 3 [11]) emetogenic chemotherapeutic agents on day 1 only. With a performance status of 0–2 and an estimated life expectancy of at least 3 months, patients met the following laboratory criteria: white blood cell count $\geq 3{,}000/mm^3$ and neutrophil count $\geq 1{,}500/mm^3$; platelet count $\geq 100{,}000/mm^3$; AST (GOT) and ALT (GPT) $\leq 1.5 \times$ upper limit of the normal range at the facility; ALP $\leq 2.5 \times$ upper limit of the normal range at the facility; total bilirubin ≤ 1.5 mg/dL; and creatinine ≤ 1.5 mg/dL. The following patients were excluded from the study: patients with a risk of vomiting for other reasons (symptomatic brain metastasis, meningeal infiltration, epilepsy, active peptic ulcer, gastrointestinal obstruction, concomitant abdominal or pelvic radiotherapy, etc.); and pregnant, nursing, or possibly pregnant women. After the protocol and informed consent form were approved by the institutional review board (IRB) at the facility, patients who gave written informed consent were enrolled. All studies were conducted in accordance with the principles of Good Clinical Practice (GCP) and the basic principles of the Declaration of Helsinki.

Design and treatment

This was an open-label study. A total of 20 patients were randomized to receive aprepitant at an oral dose of 125/80 mg (125 mg on day 1 and 80 mg on days 2–5; $n = 10$) or 40/25 mg (40 mg on day 1 and 25 mg on days 2–5; $n = 10$). In addition, all patients received standard antiemetic therapy consisting of intravenous granisetron (40 μg/kg on day 1) and intravenous dexamethasone sodium phosphate (on days 1–3). In this study, the dose of intravenous dexamethasone was 6 mg on day 1 and 4 mg on days 2 and 3 in the 125/80-mg group and 8 mg on day 1 and 6 mg on days 2 and 3 in the 40/25 mg group. Although, in the antiemetic guidelines [4–6], it is recommended that dexamethasone is administered at a dose of 12 mg on day 1 and at a dose of 8 mg on day 2 and thereafter in combination with aprepitant 125/80 mg, the dose of dexamethasone in this study was determined in order to compare the clearance of dexamethasone in this study with that obtained from Japanese cancer patients in the absence of aprepitant at a dose of 12 mg dexamethasone on day 1 [10].

Pharmacokinetic evaluation

Blood samples for measurement of plasma aprepitant concentration were collected before administration of aprepitant on days 1–5 and 1, 2, 3, 5, 9, 11, and 24 h after administration of aprepitant on day 1 and on day 5 only. In addition, a separate set of blood samples for measurement of plasma dexamethasone concentration were collected immediately, 15 min, 30 min, and 1.5, 3.5, 7.5, 9.5, and 22.5 h after administration of dexamethasone on day 1.

Methods for measurement of plasma aprepitant and dexamethasone concentrations

For each subject, venous blood was collected in an EDTA 2Na-treated tube at each sampling time point and immediately centrifuged at approximately 1,500*g* (approximately 3,000 rpm) for 10 min at room temperature. Then, the resultant plasma was transferred to a polypropylene tube and stored frozen at −20°C. The plasma concentrations of aprepitant and dexamethasone were measured by liquid chromatography/tandem mass spectrometry (LC/MS/MS). After methanol was added to plasma, the internal standard and carbonate buffer (for aprepitant) or ammonium acetate buffer (for dexamethasone) were added and mixed. Then, *t*-butyl methyl ether (for aprepitant) or diethyl ether (for dexamethasone) was added to and mixed with the plasma sample and centrifuged. After the aqueous layer was frozen in a methanol/dry ice bath, the entire organic layer was collected in a tube and placed under

nitrogen stream at approximately 40°C to remove the solvent. The residue was suspended in ammonium acetate aqueous solution (containing formic acid)/acetonitrile (for aprepitant) or methanol/water (for dexamethasone) for use in LC/MS/MS.

The pharmacokinetic parameters of aprepitant and dexamethasone were calculated by non-compartment analysis using WinNonlin Professional® software Ver.4.0.1 (Pharsight Corporation, Mountain View, CA, USA). The maximum plasma concentration (C_{max}), time to maximum plasma concentration (t_{max}), and area under the plasma concentration–time curve from 0 to 24 h post-dose ($AUC_{0-24\ h}$) were calculated for aprepitant, and the C_{max}, area under the plasma concentration–time curve from 0 to infinity ($AUC_{0-\infty}$), $t_{1/2}$, total clearance (CL_{tot}), and volume of distribution at steady state (V_{ss}) were calculated for dexamethasone.

Assessment of substance P

Before administration of aprepitant on days 1–5, venous blood was collected in an ethylenediaminetetraacetic acid (EDTA)/aprotinin-treated tube from each subject and inverted to mix. After blood was immediately centrifuged at 1,500*g* (approximately 3,000 rpm) for 10 min at 4°C, 0.5 mL of plasma was stored frozen at –20°C. The plasma substance P concentration was measured by enzyme immunoassay (EIA).

Statistical analysis

To assess ethnic differences in the pharmacokinetics of aprepitant, the C_{max} and $AUC_{0-24\ h}$ at a dose of 125 mg in Japanese cancer patients were compared with those in non-Japanese cancer patients [12] by calculating the geometric mean ratio (Japanese/non-Japanese) and its 90% confidence interval for each parameter.

To assess the validity of adjusting the dose of dexamethasone in the 125/80 and 40/25 mg groups, the exposure levels of dexamethasone were compared. The C_{max} and $AUC_{0-\infty}$ of dexamethasone in each group were used to calculate the geometric mean ratio (125/80 mg group/40/25 mg group) and its 90% confidence interval for each parameter. In addition, the clearance of dexamethasone in each group was compared with that calculated in the absence of aprepitant in Japanese cancer patients [10].

For substance P, the plasma concentration on each measurement day was used to assess the change on day 2 and thereafter, and these changes were evaluated by paired *t* test.

This study was designed and funded by Ono pharmaceutical Co., Ltd. and Merck & Co., Inc., the manufacturer of aprepitant.

Results

Patients

A total of 20 patients (10 in the 125/80 mg group and 10 in the 40/25 mg group) were included. Patients' characteristics are shown in Table 1. There were 18, 1, and 1 patients with non–small cell lung cancer, small-cell lung cancer, and mesothelioma, respectively. All were treated with at least the highly emetogenic chemotherapeutic agent cisplatin (≥70 mg/m^2). The two groups were generally similar in age, sex, height, and body weight.

Pharmacokinetics of aprepitant

All 20 enrolled patients were included in the pharmacokinetic analysis. The pharmacokinetic parameters of aprepitant are shown in Table 2. In the 125/80 mg group, the $AUC_{0-24\ h}$ on days 1 and 5 increased out of proportion to the dose, compared with that in the 40/25 mg group.

The geometric mean ratio and its 90% confidence interval (CI) of the C_{max} and $AUC_{0-24\ h}$ of aprepitant in Japanese cancer patients to non-Japanese cancer patients was 1.09 (0.79–1.52) and 1.12 (0.87–1.45), respectively,

Table 1 Characteristics of patients

Characteristics	125/80 mg regimen $n = 10$	40/25 mg regimen $n = 10$
Male/female (*N*)	6/4	7/3
Age (years)		
Mean (S.D.)	59.7 (6.7)	63.6 (5.9)
Range	47–71	55–72
Height (cm)		
Mean (S.D.)	161.16 (9.91)	161.24 (12.97)
Range	147.0–179.5	139.2–177.3
Weight (kg)		
Mean (S.D.)	55.72 (10.28)	56.86 (14.17)
Range	42.2–76.6	42.4–82.7
Primary cancer diagnosis (*N*)		
Non–small cell lung cancer	9	9
Small-cell lung cancer	1	0
Mesothelioma	0	1
Chemotherapy regimen (*N*)		
Cisplatin + gemcitabine	3	5
Cisplatin + tegafur/gimeracil/oteracil	2	2
Cisplatin + vinorelbine	2	2
Cisplatin + etoposide	2	0
Cisplatin + docetaxel	1	1

Table 2 Summary of the pharmacokinetics of aprepitant on days 1 and 5

Day	Parameter	125/80 mg regimen	40/25 mg regimen
1	C_{max} (ng/mL)	2,210 ± 870	536 ± 105
	T_{max} (h)	7.0 (3.0–9.0)	3.0 (2.0–9.0)
	$AUC_{0-24\ h}$ (ngh/mL)	30,000 ± 8,700	6,360 ± 1,350
5	C_{max} (ng/mL)	3,070 ± 850	453 ± 109
	T_{max} (h)	3.0 (2.0–9.0)	3.0 (2.0–3.0)
	$AUC_{0-24\ h}$ (ngh/mL)	46,000 ± 17,100	5,420 ± 1,680

Mean ± SD, T_{max} median (range)

C_{max}, maximum plasma concentration, T_{max}, time to maximum plasma concentration, $AUC_{0-24\ h}$ area under plasma concentration–time curve from 0 to 24 h post-dose

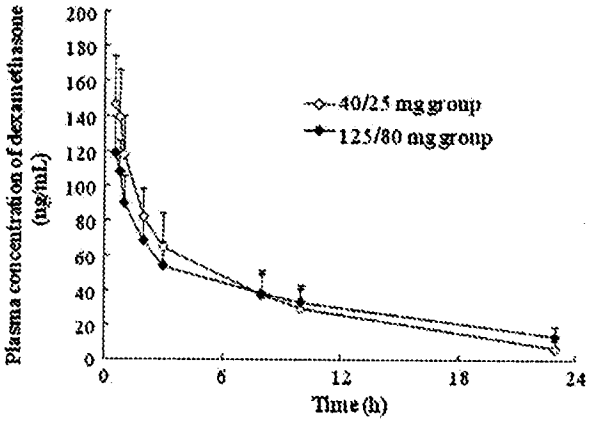


Fig. 1 Time profile of plasma dexamethasone concentration in each treatment group (day 1). Mean + SD ($n = 10$)

showing little differences between Japanese and non-Japanese groups in the pharmacokinetics of aprepitant.

Pharmacokinetics of dexamethasone

For dexamethasone, the pharmacokinetic parameters and time profile of plasma concentration on day 1 in the 125/80 and 40/25 mg groups are shown in Table 3 and Fig. 1, respectively. The geometric mean ratio (90% CI) of C_{max} and $AUC_{0-\infty}$ of dexamethasone on day 1 in the 125/80 mg group to the 40/25 mg group was 0.83 (0.73–0.94) and 1.15 (0.88–1.50), respectively, showing that although the C_{max} tended to be high in the 40/25 mg group, the $AUC_{0-\infty}$ was similar between the two treatment groups. To verify the dose reduction of dexamethasone in cancer patients who receive emetogenic cancer chemotherapy in combination with aprepitant, we compared the clearances of dexamethasone in this study with that obtained from Japanese cancer patients in the absence of aprepitant at a dose of 12 mg on day 1 (13.3 L/h) [10]. In the 125/80 and 40/25 mg groups (dexamethasone at a dose of 6 and 8 mg on day 1, respectively), the clearance of dexamethasone was 6.48 and 10.0 L/h, respectively. That is, the clearances of dexamethasone in the 125/80 and 40/25 mg groups decrease by approximately 52 and 25%, respectively. These results demonstrate the validity of reducing the dose of dexamethasone by 50 and 25% in the 125/80 and 40/25 mg groups, compared with the dose of dexamethasone in the absence of aprepitant.

Table 3 Pharmacokinetic parameters of dexamethasone in each treatment group (on day 1)

Parameter	125/80 mg regimen (Dexamethasone 6 mg)	40/25 mg regimen (Dexamethasone 8 mg)
C_{max} (ng/mL)	121 ± 17	147 ± 27
AUC_{0-t} (ngh/mL)	823 ± 213	838 ± 253
$AUC_{0-\infty}$ (ngh/mL)	1,020 ± 300	899 ± 287
$t_{1/2}$ (h)	9.6 ± 2.4	5.7 ± 1.4
CL_{tot} (L/h)	6.48 ± 2.50	10.0 ± 4.1
V_{ss} (L)	74.6 ± 14.3	65.5 ± 11.7

Mean ± SD

C_{max} maximum plasma concentration, AUC_{0-t}, area under plasma concentration–time curve from 0 to the last measurable concentration, $AUC_{0-\infty}$, area under plasma concentration–time curve from 0 to infinity, $t_{1/2}$ elimination half-life, CL_{tot} total clearance, V_{ss} volume of distribution at steady state

Evaluation of plasma substance P

The time profile of plasma substance P concentration after administration of chemotherapeutic agents in all 20 patients (days 1–5) is shown in Fig. 2. The substance P

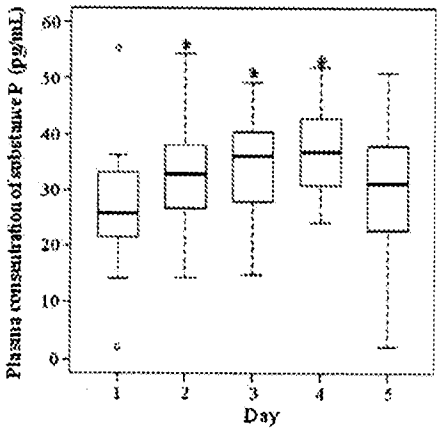


Fig. 2 Time profile of plasma substance P concentration ($n = 20$). *Top bar* highest value in the range of quartile × 1.5; *lower bar* lowest value in the range of quartile × 1.5; *top of box* upper quartile; *bottom of box* lower quartile; middle bar: median value; *circles* outliers $^*P < 0.05$ compared with baseline (day 1) concentration

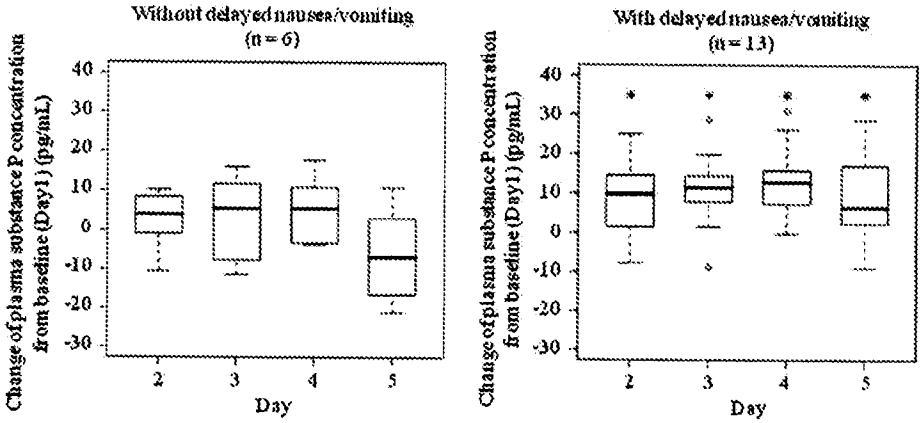


Fig. 3 Change in plasma substance P concentration ($n = 19$). *Top bar* highest value in the range of quartile × 1.5; *lower bar* lowest value in the range of quartile × 1.5; *top of box* upper quartile; *bottom of box* lower quartile; *middle bar* median value; *circles* outliers $*P < 0.05$ between days 2 and 5 compared with baseline (day 1)

concentration significantly increased on days 2–4, compared with that on day 1 (baseline) ($P < 0.05$, paired t test).

There was no difference in the change in the plasma substance P concentration between the 125/80 and 40/25 mg groups (data not shown). The change in substance P concentration in plasma from baseline (the concentration before the start of treatment with aprepitant) in patients with or without delayed nausea/vomiting is shown in Fig. 3. One patient had missing data for the substance P concentration on day 1, and so we analyzed the change in substance P concentration from baseline (day 1) in 19 patients. In patients with delayed nausea/vomiting, substance P concentration increased significantly between days 2 and 5 compared with baseline (day 1) ($P < 0.05$, paired t test). On the other hand, in patients without delayed nausea/vomiting, the increase in substance P concentration on days 2–5 was not statistically significant.

Discussion

In this study, the pharmacokinetics of aprepitant and dexamethasone were determined in Japanese cancer patients receiving emetogenic chemotherapeutic agents. There were no differences in the pharmacokinetics of aprepitant between Japanese and non-Japanese cancer patients. In addition, we showed the validity of dose adjustment of dexamethasone used in combination with aprepitant (i.e., reducing the dose of dexamethasone by 50% when combined with 125 mg of aprepitant). We also found that the blood concentration of substance P, which is deeply involved in the pharmacological effects of aprepitant, increased after administration of chemotherapeutic agents.

In the present study, the geometric mean ratio of the C_{max} and $AUC_{0-24\ h}$ in Japanese cancer patients to non-Japanese cancer patients was 1.09 and 1.12, respectively, indicating no ethnic differences in the pharmacokinetics of aprepitant. In the aprepitant 125/80 mg group, more than dose-proportional increase in $AUC_{0-24\ h}$ occurred on both days 1 and 5, compared with that in the 40/25 mg group. Aprepitant is primarily metabolized by CYP3A4 [13], and this more than proportional increase in the $AUC_{0-24\ h}$ of aprepitant may reflect saturated metabolism of aprepitant via CYP3A4 as previously reported in healthy non-Japanese volunteers [14].

In this study, granisetron hydrochloride and dexamethasone sodium phosphate were concomitantly used as standard antiemetic therapy. Aprepitant–dexamethasone interaction causes the increase in plasma dexamethasone concentration [9], and it has been suggested that this drug interaction may also cause a slight increase in the incidence of infection-related serious adverse events [15]. Since the AUC of dexamethasone (p.o.) has been shown to increase approximately two times after administration of aprepitant at a dose of 125 mg on day 1 in healthy adults [9], the dose of dexamethasone has to be reduced by 50% when used in combination with 125 mg of aprepitant. While oral dexamethasone was used in the report by McCrea et al. [9], this was the first full pharmacokinetic study of intravenous administration of dexamethasone when used in combination with aprepitant in cancer patients actually receiving chemotherapeutic agents. In the 125/80 mg group, the clearance of intravenous dexamethasone decreased by approximately 52% from that calculated in the absence of aprepitant, justifying a 50% dose reduction of intravenous dexamethasone used in combination with 125 mg of aprepitant in cancer patients as McCrea et al. demonstrated in healthy adults [9]. And the results from this full pharmacokinetic study also supported a report using a population pharmacokinetics model by Nakade et al. [10] that the clearance of intravenous dexamethasone used in combination with aprepitant at a dose of 125 mg decreased by 47.5% of that in the absence of aprepitant.

While aprepitant may exert its antiemetic effect during chemotherapy, by inhibiting the binding of substance P to

the NK_1 receptor in the vomiting center [1], few studies have been conducted to investigate the relationship between the blood pharmacokinetics of substance P and nausea/vomiting during treatment with chemotherapeutic agents in humans. Substance P has been shown to be co-localized with serotonin in enterochromaffin cells in the gastrointestinal tract [16] and cross the blood–brain barrier in animals [17]. These reports raise the possibility that substance P of peripheral origin may act centrally to induce emesis. However, it is still not shown whether exocytotic release of substance P from enterochromaffin cells in the gastrointestinal tract occurs after administration of emetogenic agents. This study showed that the plasma substance P concentration significantly increased on days 2–4 after administration of chemotherapeutic agents. It was also shown that the plasma substance P concentration significantly increased only in patients with delayed nausea/vomiting. These results, as well as the report from Higa [18], support the possibility that the elevation of the plasma substance P concentration by emetogenic chemotherapeutic agents may be involved in the pathogenesis of CINV, especially in the delayed phase. The plasma substance P concentration ranged from 0 to 1,608 pg/mL in a report by Higa et al. [18] and from 2–55 pg/mL in the present study. The cause of this difference is unknown, but may be attributed to different assay kits used to measure the substance P concentration (Higa et al. used R&D systems, and we used Cayman Chemical).

In conclusion, this study demonstrated similar plasma pharmacokinetics of aprepitant in Japanese and non-Japanese, the validity of reducing dexamethasone dose, and the existence of increased substance P concentration in patients receiving highly emetogenic cancer chemotherapy. Further studies are required to clarify whether measurement of the plasma pharmacokinetics of substance P may be a clinically meaningful marker for CINV in patients receiving emetogenic agents.

Conflict of interest None.

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References

1. Tattersall FD, Rycroft W, Cumberbatch M, Mason G, Tye S, Williamson DJ, Hale JJ, Mills SG, Finke PE, MacCoss M, Sadowski S, Ber E, Cascieri M, Hill RG, MacIntyre DE, Hargreaves RJ (2000) The novel NK1 receptor antagonist MK-0869 (L-754, 030) and its water soluble phosphoryl prodrug, L-758, 298, inhibit acute and delayed cisplatin-induced emesis in ferrets. Neuropharmacology 39:652–663
2. Warr DG, Grunberg SM, Gralla RJ, Hesketh PJ, Roila F, Wit R, Carides AD, Taylor A, Evans JK, Horgan KJ (2005) The oral NK_1 antagonist aprepitant for the prevention of acute and delayed chemotherapy-induced nausea and vomiting: pooled data from 2 randomised, double-blind, placebo controlled trials. Eur J Cancer 41:1278–1285
3. Warr DG, Hesketh PJ, Gralla RJ, Muss HB, Herrstedt J, Eisenberg PD, Raftopoulos H, Grunberg SM, Gabriel M, Rodgers A, Bohidar N, Klinger G, Hustad CM, Horgan KJ, Skobieranda F (2005) Efficacy and tolerability of aprepitant for the prevention of chemotherapy-induced nausea and vomiting in patients with breast cancer after moderately emetogenic chemotherapy. J Clin Oncol 23:2822–2830
4. Kris MG, Hesketh PJ, Somerfield MR, Feyer P, Clark-Snow R, Koeller JM, Morrow GR, Chinnery LW, Chesney MJ, Gralla RJ, Grunberg SM (2006) American society of clinical oncology guideline for antiemetics in oncology: update 2006. J Clin Oncol 24:2932–2947
5. Rolia F, Hesketh PJ, Herrstedt J (2006) The Antiemetic Subcommittee of the Multinational Association of Supportive Care in Cancer (MASCC). Prevention of chemotherapy- and radiotherapy-induced emesis: results of the 2004 Perugia international antiemetic consensus conference. Ann Oncol 17:20–28
6. NCCN Clinical practice guidelines in oncology™ (2007) Antiemesis V.1
7. Blum RA, Majumdar A, McCrea J, Busillo J, Orlowski LH, Panebianco D, Hesney M, Petty KJ, Goldberg MR, Murphy MG, Gottesdiener KM, Hustad CM, Lates C, Kraft WK, Van Buren S, Waldman SA, Greenberg HE (2003) Effects of aprepitant on the pharmacokinetics of ondansetron and granisetron in healthy subjects. Clin Ther 25:1407–1419
8. Shah AK, Hunt TL, Gallagher SC, Cullen MT Jr (2005) Pharmacokinetics of palonosetron in combination with aprepitant in healthy volunteers. Curr Med Res Opin 21:595–601
9. McCrea JB, Majumdar AK, Goldberg MR, Iwamoto M, Gargano C, Panebianco DL, Hesney M, Lines CR, Petty KJ, Deutsch PJ, Murphy MG, Gottesdiener KM, Goldwater DR, Blum RA (2003) Effects of the neurokinin$_1$ receptor antagonist aprepitant on the pharmacokinetics of dexamethasone and methylprednisolone. Clin Pharmacol Ther 74:17–24
10. Nakade S, Ohno T, Kitagawa J, Hashimoto Y, Katayama M, Awata H, Kodama Y, Miyata Y (2008) Population pharmacokinetics of aprepitant and dexamethasone in the prevention of chemotherapy-induced nausea and vomiting. Cancer Chemother Pharmacol 63:75–83
11. Hesketh PJ, Kris MG, Grunberg SM, Beck T, Hainsworth JD, Harker G, Aapro MS, Gandara D, Lindley CM (1997) Proposal for classifying the acute emetogenicity of cancer chemotherapy. J Clin Oncol 15:103–109
12. Nygren P, Hande K, Petty KJ, Fedgchin M, van Dyck K, Majumdar A, Panebianco D, de Smet M, Ahmed T, Murphy MG, Gottesdiener KM, Cocquyt V, van Belle S (2005) Lack of effect of aprepitant on the pharmacokinetics of docetaxel in cancer patients. Cancer Chemother Pharmacol 55:609–616
13. Sanchez RI, Wang RW, Newton DJ, Bakhtiar R, Lu P, Chiu SH, Evans DC, Huskey SE (2004) Cytochrome P450 3A4 is the major enzyme involved in the metabolism of the substance P receptor antagonist aprepitant. Drug Metab Dispos 32:1287–1292
14. Majumdar AK, Howard L, Goldberg MR, Hickey L, Constanzer M, Rothenberg PL, Crumley TM, Panebianco D, Bradstreet TE, Bergman AJ, Waldman SA, Greenberg HE, Butler K, Knops A, De Lepeleire I, Michiels N, Petty KJ (2006) Pharmacokinetics of

aprepitant after single and multiple oral doses in healthy volunteers. J Clin Pharmacol 46:291–300
15. Chawla SP, Grunberg SM, Gralla RJ, Hesketh PJ, Rittenberg C, Elmer ME, Schmidt C, Taylor A, Carides AD, Evans JK, Horgan KJ (2003) Establishing the dose of the oral NK1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting. Cancer 97:2290–2300
16. Heitz P, Polak JM, Timson DM, Pearse AG (1976) Enterochromaffin cells as the endocrine source of gastrointestinal substance P. Histochemistry 49:343–347
17. Freed AL, Audus KL, Lunte SM (2001) Investigation of substance P transport across the blood-brain barrier. Peptides 23:157–165
18. Higa GM, Auber ML, Altaha R, Piktel D, Kurian S, Hobbs G, Landreth K (2006) 5-Hydroxyindoleacetic acid and substance P profiles in patients receiving emetogenic chemotherapy. J Oncol Pharm Pract 12:201–209

The Pharmaceutics and Compounding Laboratory

Emulsions: Preparation and Stabilization

Objectives

Introduction

Emulsifying Agents

Methods of Emulsion Preparation

- Continental
- English
- Bottle
- Beaker
- Auxiliary

Resources

Methods of Emulsion Preparation

Commercially, emulsions are prepared in large volume mixing tanks and refined and stabilized by passage through a colloid mill or homogenizer. Extemporaneous production is more concerned with small scale methods. Several methods are generally available to the pharmacist. Each method requires that *energy* be put into the system in some form. The energy is supplied in a variety of ways: trituration, homogenization, agitation, and heat.

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Research Article

Formulation, preparation, and stability of intravenous bufadienolides-loaded lipid microspheres

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The purpose of this study was to develop a new formulation of intravenous lipid microspheres for bufadienolides (bufadienolides-loaded lipid microspheres, BU-LM) and investigate the stability of BU-LM after dilution and long-term storage. Photon correlation spectroscopy, electrophoretic light scattering, and light microscopy were used to evaluate the physical characteristics of BU-LM. The chemical properties of bufadienolides were measured by high-performance liquid chromatography. The optimum BU-LM, consisting of 10% MCT, 3.0% Lipoid S75, 0.4% F68, 0.05% sodium oleate and 2.5% glycerol, was prepared by emulsification with a high-speed shear mixing at 10 000 rpm for 12 min and a high-pressure homogenization at 800 bar for 8 cycles at 30°C. The BU-LM at pH 6.48, with the particle size distribution of 175.2 ± 57.3 nm, ζ-potential of −32.10 mV, entrapment efficiency of 86.9%, 91.7%, 92.9%, and contents of 20.8%, 31.3%, 50.4% for B, C, R, respectively, was stable after sterilization in a 121°C rotating autoclave water steam bath for 10 min. Moreover, BU-LM had sufficient physicochemical stability after dilution with 5% glucose injection and long-term storage at 4 ± 2°C for 18 months. BU-LM has a great potential for clinical applications as a new drug delivery system for bufadienolides.

Practical applications: Bufadienolides, mainly composed of bufalin (B), cinobufagin (C), and resibufogenin (R) have poor aqueous solubility and are chemically unstable. Currently the main marketable products of bufadienolides are solution injections, which cause serious venous irritation and in this formulation, the drug is not protected from degradation. Lipid microspheres, with the unique properties of a low cost, low toxicity, good storage stability, easy to scale up production, sustained release and targeting effect, incorporate the drugs into the interior oil phase and the oil-water interfacial film; thus a direct contact of the drug with body fluids and tissues is prevented, which increases the stability of the drugs and minimizes the possible side effects.

Keywords: Bufadienolides / Formulation / Lipid microsphere / Preparation / Stability

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1 Introduction

Chan Su (toad venom), the traditional Chinese medicine, is obtained from the postauricular and skin glands of Chinese toads. It has been used as a cardiotonic, diuretic, anodyne and hemostatic agent [1] in China, Japan and other Asian countries for centuries, and over the last decade, it has gained considerable favor in the United States and elsewhere [2].

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Abbreviations: B, bufalin; **C,** cinobufagin; **R,** resibufogenin; **HPLC,** high-performance liquid chromatography; **BU-LM,** bufadienolides-loaded lipid microsphere; **BU-S,** bufadienolides-loaded aqueous solution; **EE,** entrapment efficiency; **DDW,** double-distilled water; **MCT,** medium-chain triglyceride; **LCT,** long-chain triglyceride; **SO,** sodium oleate; **PSD,** particle size distribution; **PC,** phosphatidylcholine; **RT,** room temperature

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The major effective components, generally called bufadienolides, have a novel steroidal A/B *cis* and C/D *cis* structure with an α-pyrone ring at C-17 and a β-hydroxyl at C-3 position, which exhibit a range of biological activities, such as cardiotic, blood pressure stimulating, respiration, and antineoplastic activities. Of the bufadienolides, bufalin (B), cinobufagin (C), and resibufogenin (R), shown in Fig. 1, are three typical bufadienolides and have the promising prospect as antineoplastic agents [3]. However, they have poor aqueous solubility and chemical stability. In current, commercially marketable products of bufadienolides are mainly Toad Venom Injection and Huachansu Injection, but their usages are limited by two problems. On one hand, the intravenous aqueous solution causes venous irritation, which results in serious pain in some patients. On the other hand, none of these can effectively reduce the degradation of bufadienolides. Therefore, in order to ensure both high solubility and stability of the drug, it is of great importance to develop a new dosage form for intravenous administration of bufadienolides.

Over the last few decades, lipid microspheres (LMs), liposomes and nanoparticles have been attracting increasing attention as drug delivery systems for poorly water-soluble drugs because of their drug targeting effect and therapeutic benefit. However, liposomes are relatively unstable, also the enormous cost and complexity associated with the manufacturing process often limit their commercial viability. Similar problems exist in nanoparticles. And besides, great toxicity of the polymer in nanoparticles cannot be avoided. Nevertheless, it is distinctly different that LMs, also called lipid emulsions or microemulsions, have been considered promising parenteral drug delivery systems, attributable to the unique properties of low cost, low toxicity, good storage stability and easy large-scale production [3]. LMs can also enhance the solubility and stability of the drugs to obtain sustained release and targeting by incorporating the drugs into the interior oil phase and the oil-water interfacial film [4]. In addition, LMs can prevent direct contact of the drug with body fluids and tissues to minimize the possible side effects.

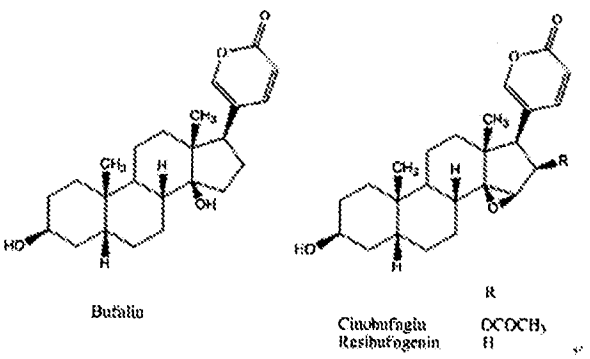


Figure 1. Chemical structures of three kinds of bufadienolides.

All these excellent characteristics may make the LMs be an attractive carrier for bufadienolides. Thus, in our study, BU-LM were developed and investigated. Firstly, the formulation and preparation procedures of BU-LM were systemically studied, then the stability of BU-LM after long-term storage at 4 ± 2°C over 18 months and dilution with 0.9% sodium chloride injection and 5% glucose injection for 4 h were investigated in detail.

2 Materials and methods

2.1 Materials

Bufadienolides were extracted from toad venom in the Department of Pharmaceutics, Shenyang Pharmaceutical University, P. R. China. Bufadienolides (purity 95% above) mainly consist of B, C and R with a mass ratio of 2:3:5. The molecular weights of B, C and R are 386.5, 442.5, and 384.5, respectively.

The following materials were purchased or obtained from the sources in parentheses: Lipoid S75®, Lipoid E80®, sodium oleate (SO) and medium-chain triglycerides (MCT) (Lipoid KG, Ludwigshafen, Germany), PL-100M (Q.P. Co., Tokyo, Japan), long-chain triglyceride (LCT) (Tieling Beiya Pharmaceutical Co., Liaoning, China), Tween80 for parenteral use (Shenyu Medicine and Chemical Industry Ltd. Co., Shanghai, China), Poloxamer188 (F-68) (BASF AG, Ludwigshafen, Germany), and glycerin (Suichang Glycerin Plant, Zhejiang, China). Double-distilled water (DDW) was used in all experiments and all other chemicals and reagents used were of analytical or chromatographic grade.

2.2 Methods

2.2.1 Preparation of BU-LM

The BU-LM with a concentration of 0.5 mg/mL was prepared by high-pressure homogenization. Firstly, 3.0% (w/v) Lipoid S75 was dispersed in 10% (w/v) MCT at 78 ± 2°C in a constant temperature water bath (HH.SY11-Ni, Hangfeng Apparatus and Instrument Co., Beijing, China) until dissolved, then the bufadienolides were added and stirred for another 20 min to prepare the oil phase. The aqueous phase, consisting of 2.5% (w/v) glycerol, 0.4% (w/v) F-68 and 0.05% (w/v) SO, was also heated at 70 ± 2°C in another water bath until uniformly dissolved. Then, the oil phase was added slowly to the aqueous phase with high-speed shear mixing (ULTRA RURRAX®IKA® T18 basic, Germany) at 10 000 rpm to obtain the coarse emulsion. The high-speed shear mixing process was carried out for 12 min with a 3-min high speed-shear mixing-on period and a 1-min-off period. Thirdly, the volume was adjusted with DDW, and the pH with 0.1 mol/L HCl to 6.5. After that, the coarse emulsion was subjected to high-pressure homogenization (Niro Soavi NS 10012K homogenizer, Via M. da Erba, 29/A-43100

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PARMA, Italy) at 800 bar for eight cycles. The temperature of the entire homogenization process was controlled at 30°C using an ice-water bath. Finally, the BU-LMs were sealed in vials, and sterilized in a 121°C rotating autoclave water steam bath for 10 min.

2.2.2 Investigations of BU-LM

2.2.2.1 Formulation investigations of BU-LM

The composition and ratio of the oil phase (LCT and MCT), the types and amounts of the emulsifiers (soybean lecithin Lipoid S75, egg yolk lecithin Lipoid E80, and PL-100M) and co-emulsifiers (Tween80, F68 and SO), the addition of the osmotic agent (glycerol) were employed to investigate the influence of different compositions of formulation on the physical and chemical stability of BU-LM. The BU-LMs were prepared according to Section 2.2.1 with one condition changed while the others constant.

2.2.2.2 Preparation investigations of BU-LM

To prepare BU-LM with the optimized physicochemical properties, the processes of high-speed shear mixing, high-pressure homogenization, thermal sterilization, temperature, and pH were also investigated in details. The BU-LMs were prepared according to Section 2.2.1 with one condition changed while the others constant.

2.2.3 Characteristics of BU-LM

2.2.3.1 Particle size distribution, zeta potential and pH

The mean particle size and SD of BU-LM, used to evaluate the particle size distribution (PSD) and polydispersity index (PI) of BU-LM, were determined by photon correlation spectroscopy (PCS; dynamic light scattering, DLS) using a Nicomp™ 380 Particle Sizing system (Zeta Potential/Particle Sizer Nicomp™ 380ZLS, Santa Barbara, California, USA). The system was sensitive to particles with size ranging from 5 nm to 3 μm. The BU-LM sample was diluted 1:5000 with DDW immediately before measurement at 25°C. The Nicomp and Gaussian distributions of particle size were obtained at the same time with intensity weighting, volume-weighting, and number-weighting. The particle size analysis in this study was all evaluated using the intensity-weighting Gaussian distribution pattern unless otherwise specified. In addition, the microscopic assessment was carried out using a Motic DMBA450 microscope (MoticChina Group Co. Ltd., Beijing, China). The emulsion samples were analyzed without being diluted using an oil immersion microscope with 1,000-fold magnification; typically, 20 microscopic fields were analyzed for the detection of the number of large droplets exceeding 5 μm.

The pH of BU-LM was measured using a pH meter (Leici®, Shanghai Precision Science Instrument Ltd., Shanghai, China) fitted with a microelectrode at 25 ± 2°C.

2.2.3.2 Entrapment efficiency (EE) of bufadienolides in BU-LM

Ultracentrifugation method was used to determine the EE of BU-LM by measuring the concentrations of B, C, and R in the dispersion phase. Firstly, the sample of BU-LM was put in the polyallomer tube and ultracentrifugated at 4°C using a CS120GXL ultracentrifuge (HITACHI Co. Japan) at 50 000 rpm for 1.5 h. Then, the bottom of the tube was pricked with a syringe needle to collect the aqueous phase. Lastly, the amounts of B, C, and R in the separated aqueous phase were measured by high-performance liquid chromatography (HPLC), and the EEs were calculated according to the following equation.

$$\mathrm{EE}\,(\%) = \frac{C_{\mathrm{total}}V_{\mathrm{total}} - C_{\mathrm{water}}V_{\mathrm{water}}}{C_{\mathrm{total}}V_{\mathrm{total}}} \times 100$$

where C_{total} and V_{total} were the concentration and the volume of the drug in the whole BU-LM, and the C_{water} and V_{water} were those in the water phase, respectively.

2.2.4 High-performance liquid chromatography (HPLC) analysis

A RP HPLC analytical method was employed for the analysis of BU-LM. The HPLC system (Hitachi) consisted of an autosampler (L-7200), four pumps (L-7100), and a UV–VIS detector (L-7420), all interfaced with D-7000 HSM software along with an HiQ sil C18 column (250 × 4.5 mm, i.d. 4 μm; KYA TECH Corporation, Tokyo, Japan) and a precolumn (Fusion-RP 4 × 3.0 mm). The mobile phase was a 45:55 (v/v) mixture of acetonitrile:-water (pH 3.2) containing 0.5% potassium dihydrogen phosphate at a flow rate of 1.0 mL/min. The wavelength was 296 nm, the injection volume was 10 μL and the column temperature was 40°C. The sample of BU-LM was diluted with isopropanol and passed through a 0.22-μm micropore membrane filter before injection into the column.

2.2.5 Stability study

2.2.5.1 Dilution stability of BU-LM

The physical stabilities of BU-LM in 5% glucose (Glu) and 0.9% sodium chloride (NaCl) injections were investigated. The PSD and 99% cumulative distribution were determined at 0, 0.5, 1, 2, 3, and 4 h after being diluted to 5-fold and 10-fold with 5% Glu or 0.9% NaCl injection at room temperature (RT), respectively.

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2.2.5.2 *Long-term stability of BU-LM*

The long-term stability assessment of BU-LM was monitored over 18 months at 4 ± 2°C. At pre-determined time intervals, samples were removed and allowed to reach the RT. Their physicochemical properties were evaluated by the physical appearance, PSD, ζ-Potential, pH, EE and drug remaining. All the studies were performed in triplicate.

3 Results and discussion

3.1 Formulation investigations of BU-LM

3.1.1 Oil phase composition and ratio of BU-LM

The oil phase composition in emulsions plays an important role in emulsion formulations. Normally, LCT and MCT are employed mainly as the oil phase in fat emulsions intended for total parenteral nutrition [5]. Hence, the 10% (w/v) oil phases of LCT, MCT and their mixture at ratio of 5%:5% were employed to investigate the effect of different oil phases on physicochemical stability of BU-LM, including the physical appearance, PSD and EE. According to Table 1, oil droplets were observed in the Formulations with LCT after sterilization, and with the increase of LCT from 5 to 10%, the oil droplets became more and larger. The explanation for this phenomenon was that the longer the hydrocarbon chain length of the dispersed oil phase, the greater the interfacial tension against the continuous aqueous phase, the more unstable the emulsion is [6]. When the oil phase was pure 10% MCT in Formulation 3, BU-LM displayed good physicochemical characteristics, with PSD of 166.6 ± 61.8 nm and EEs of 85.4, 91.6, and 93.9% for B, C and R, respectively. The high EEs might be due to the higher polarity of MCT. MCT was approximately 100 times more water-soluble than LCT and so, it had an increased drug uptake capability. Besides, the Formulation 3 had sufficient physical stability even stored at 60°C for 5 days. It had been reported that MCTs might reduce the toxicity associated with pure LCT-based lipid emulsions and provide more stable all-in-one admixtures, also they could reduce the high amount of linoleic acid, balance the fatty acid pattern and adjust the viscosity of the oil phase [7–9]. Taken together, pure MCT was selected as the oil phase in the end. However, as MCT ratio decreased from 10 to 5% in Formulation 4, the mean particle size of BU-LM became remarkably smaller while the SD of PSD almost unchanged, which led to a wider size distribution and resulted in the instability of BU-LM. In general, emulsions with the mean particle size of about 200 nm tended to be the most physically stable. Too small particle existing in the BU-LM with a very large interfacial surface had a rapid Brownian motion, which easily coalesced to big particle and led to aggregation after placed for a long time. Besides, Formulation 4 with the EE decreased 5% underwent emulsion breakage after stored at 60°C for 5 days, which might be because that 5% MCT was insufficient to encapsulate the drug effectively and form a strong oil film to remain the long-term stability of BU-LM. Hence, a 10% (w/v) MCT as the oil phase in BU-LM was employed.

3.1.2 The type and amount of lecithin as emulsifier in BU-LM

Emulsifiers are another essential component of lipid emulsions. It is well known that the emulsification depends on the emulsifiers used, and the emulsification process significantly influences the stability of the emulsion [10]. Though various emulsifiers on the market are concerned, lecithin should always be the first choice. The natural lecithins, including egg yolk lecithin and soybean lecithin, can be totally biodegraded and metabolized, so they are regarded as well-tolerated and non-toxic compounds with excellent biocompatibility, and suitable for long-term use and high-dose infusion. Lipoid S75 (phosphatidylcholine, PC 72%) as soybean lecithin, Lipoid E80 (PC 82%) and PL-100M (PC 80%) as egg yolk lecithin, were employed to investigate the influence of different types of lecithins on the properties of BU-LM. The results of our study in Table 2 showed that BU-LM prepared with egg yolk lecithin could not undergo the autoclaving sterilization, because the visible oil droplets or emulsion breakage were observed for the BU-LM with PL-100M or Lipoid E80, respectively. However, under the same condition, BU-LM with soybean lecithin Lipoid S75 exhibited a good physical appearance and higher ζ-potential of

Table 1. The influence of oil phase composition and ratio on the properties of BU-LM

				EE (%)			Physical appearance	
Formulation	LCT:MCT	PSD (nm)	PI	B	C	R	After autoclaving	After stored at 60°C for 5 days
1	10:0	ND	ND	ND	ND	ND	Bulk oil droplets	Bulk oil droplets
2	5:5	ND	ND	ND	ND	ND	Visible oil droplets	Bulk oil droplets
3	0:10	166.6 ± 61.8	0.138	85.4	91.6	93.9	Good	Good
4	0:5	137.2 ± 59.3	0.187	80.5	86.2	87.5	Good	Emulsion breaking

ND, not determined.

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Table 2. The influence of the type of lecithin on the properties of BU-LM

	3.0% (w/v) Lecithin	Before autoclaving				After autoclaving			
Formulation	Lecithin type	ζ-Potential (mV)	PSD (nm)	PI	Physical appearance	ζ-Potential (mV)	PSD (nm)	PI	Physical appearance
5	Lipoid S75	−29.15	177.0 ± 69.8	0.156	Good	−28.76	164.6 ± 70.8	0.185	Good
6	PL-100M	−21.04	164.5 ± 57.9	0.124	Good	ND	ND	ND	Visible oil droplets
7	Lipoid E80	−17.81	192.4 ± 96.2	0.250	Good	ND	ND	ND	Emulsion breaking

ND, not determined.

−28.76 mV. This could be due to the emulsification of different types of lecithins. Hansrani [11] and Yamaguchi et al. [12] had reported that the stability of lipid emulsions was influenced by the purity of the lecithin, and certain "impurities" of lecithin were necessary to form stable emulsions. In natural lecithin, the unesterified phosphatidic acid (PA) is present to a much lower extent than PC and PE (phosphatidylethanolamine), but it takes an important role in the stability of the emulsions since it can contribute to more negative ζ-potentials and, thus, increase the heat-stress or storage stability of the emulsions. Consequently, soybean lecithin containing more PA and some other ionic components than egg yolk lecithin exhibited excellent emulsifying properties [13]. Therefore, soybean lecithin of Lipoid S75 was selected as the main emulsifier in this paper.

In the following, different amounts of Lipoid S75 were also investigated. As shown in Table 3, oil droplets floating on the Formulation 8 and 9 were observed. This was because 1.20 or 1.5% (w/v) lecithin was not enough to emulsify the 10% oil phase in BU-LM. The BU-LM exhibited a good physical appearance after thermal sterilization when the amount of lecithin was up to 2.5% (w/v) and 3.0% (w/v), but the former was still insufficient to ensure the stability of BU-LM since flocculation, which was a significant indicator of the coalescence, was observed after storage at 25°C for only a week. In addition, Table 3 also suggested that the EE became higher with the increased lecithin, indicating that only 3% Lipoid S75 could encapsulate the drug entirely. Consequently, adding 3.0% (w/v) Lipoid S75 produced an emulsion with good physicochemical stability following heat-stress or storage, also PSD (165.5 ± 66.1 nm) and high EEs (all above 85%) could confirm its safety for intravenous administration. Hence, 3.0% (w/v) Lipoid S75 was chosen as the optimum amount of lecithin.

3.1.3 The co-emulsifiers of Tween80, F68, sodium oleate and their amounts

A single emulsifier of Lipoid S75 was insufficient to maintain the stability of the emulsion. The co-emulsifiers could help further emulsify the oil phase and form a tight complex interfacial film between the water phase and the oil phase to keep the emulsion stable. However, many of the non-ionic co-surfactants had led to various toxic reactions, thus their selection and incorporation should be carefully studied.

Usages of Tween80, F68 and sodium oleate for parenteral were investigated in this study. The result in Table 4 showed that the formulations with Tween80 could not undergo the autoclaving sterilization and visible oil drops were observed. This might be due to the low cloud point of Tween80. It had been established previously that emulsion formulations, containing an emulsifier with a high cloud point, were more resistant to coalescence during the autoclaving process, while formulations with a low cloud point, precipitated at the sterilization temperature leading to a breakdown of the film around the oil droplets and the coalescence of the

Table 3. The influence of the amount of Lipoid S75 on the properties of BU-LM

		After autoclaving					After storage at 25°C for a week
Formulation	Lipoid S75 (%, w/v)	PSD (nm)	PI	ζ Potential (mV)	Physical appearance	EE of B, C and R (%)	Physical appearance
8	1.2	ND	ND	ND	Bulk oil droplets	ND	Flocculation
9	1.5	ND	ND	ND	Visible oil droplets	ND	Flocculation
10	2.5	183.7 ± 63.5	0.119	−26.20	Good	71.8,80.5, 84.6	Flocculation
11	3.0	165.5 ± 66.1	0.160	−27.80	Good	86.1,91.9, 92.8	Good

ND, not determined.

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Table 4. The influence of the amount of F-68 and Tween-80 on the properties of BU-LM

Formulation	F-68 (%, w/v)	Tween-80 (w/v)	Before autoclaving PSD (nm)	PI	Physical appearance	After autoclaving PSD (nm)	PI	EE of B, C and R (%)	Physical appearance
12	0.0	0.2	165.7 ± 64.8	0.153	Good	ND	ND	ND	Visible oil droplets
13	0.2	0.2	156.4 ± 54.7	0.122	Good	ND	ND	ND	Visible oil droplets
14	0.4	0.2	153.3 ± 73.6	0.231	Good	ND	ND	ND	Visible oil droplets
15	0.2	0.0	179.2 ± 59.7	0.111	Good	170.6 ± 64.0	0.141	80.2,88.3,90.6	Good
16	0.4	0.0	174.5 ± 55.3	0.100	Good	166.3 ± 57.8	0.121	85.4,91.6,93.9	Good

ND, not determined.

droplets [14]. In addition, Jumaa et al. [15] reported that LM with only Tween80 as an emulsifier showed a remarkable erythrocyte membrane damage, but the formulations using only S75 and F68 did not. Thus, Tween80, which had a low cloud point and remarkable hemolytic activity but no extra advantages, was excluded, and F68 was selected as the co-emulsifier.

The addition of F68 was of great importance to emulsify the oil phase. Table 4 exhibited that the Formulation 15 with 0.2% of F68 had a good physical appearance and satisfactory PSD of 170.6 ± 64.0 nm after autoclaving, but the EEs were not all above 85%. This might be because that the F68 was insufficient to encapsulate the drug entirely. In Formulation 16, the good physicochemical property of BU-LM with PSD of 166.3 ± 57.8 nm and EE of 85.4%, 91.6%, 93.9% for B, C, R after autoclaving sterilization, respectively, indicated that 0.4% of F68 was essential and sufficient in BU-LM. Tadros and Vincent [16] pointed out that emulsion stability was dependent on the structure of the surfactant. F68, as a block copolymer and water-soluble non-ionic emulsifier, had a strong emulsifying effect. It could stabilize the newly created interface immediately and within only one homogenization cycle maximum dispersion had been already achieved [17]. Besides, the combination of emulsifier of Lipoid S75 and co-emulsifier of F-68 could form a close-packed mixed film to confer improved stability [10]. Therefore, the amount of F68 was fixed to be 0.4% (w/v).

Sodium oleate, a water-soluble co-emulsifier, was adsorbed or incorporated by the oil-water interfacial film to give a negative charge to the emulsion surface and enhance the electrostatic repulsion between emulsion droplets. It could not only stabilize the emulsion against coalescence, but could also decrease the granularity of emulsion particles. In addition, SO had a certain buffering capacity to reduce the pH change to a minimum [18]. Moreover, the interfacial film composed with lecithin-F68-SO was strong enough to remain the stability of the emulsion [19]. Hence, a small amount of SO was often used in commercial parenteral emulsions (Lipofundin®MCT, Abbolipid®, Schiwalipid® and others) to obtain stable formulations during the autoclaving process [20]. According to the Formulations from 17 to 19 in Table 5, it was obvious that the incorporation of 0.05% SO made an important contribution to increase the absolute value of the ζ-Potential and keep pH value nearly unchanged before and after autoclaving. However, SO was not endogenous, and the less used, the better. Therefore, 0.05% (w/v) SO should be added to prepare BU-LM.

3.1.4 The addition of osmotic agent

The aqueous phase should be augmented by the incorporation of ionic or osmotic agents, antioxidants, buffers and preservativesas as required. Isotonic adjustment (to 280–300 mOsm/kg) was important for large-volume parenterals such as the injectable fat emulsions because emulsified oil

Table 5. The effect of the addition of sodium oleate on the properties of BU-LM

Formulation	Sodium oleate (%, w/v)	Before autoclaving pH	ζ-Potential (mV)	PSD	PI	After autoclaving pH	ζ-Potential (mV)	PSD	PI
17	0	6.52	−17.55	183.7 ± 62.5	0.116	6.00	−17.67	175.5 ± 65.2	0.138
18	0.05	6.51	−25.06	174.8 ± 65.9	0.142	6.46	−26.44	168.2 ± 66.3	0.155
19	0.1	6.45	−27.64	172.3 ± 69.3	0.162	6.34	−27.95	161.0 ± 65.1	0.163

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exerted no osmotic effect. Glycerol with the ability of tonicity was preferred by the manufacturers of commercial soybean oil emulsion [Intralipid®, Soyacal® (Alpha Therapeutic, CA, USA), Travamulsion® (Baxter-Travenol,Il, USA)] and a commercial safflower oil emulsion (Liposyn®, Abbott, North Chicago, IL, USA). In addition to its contribution to tonicity, glycerol had been also shown to reduce the globule size and improve the creaming stability of o/w emulsions [21]. In our study, 2.5% (w/v) glycerin was used to adjust the osmotic pressure.

3.2 Preparation Investigations of BU-LM

3.2.1 Effect of coarse emulsion "dispersion" preparation

To prepare an O/W emulsion, the oil phase was added to the aqueous phase when both dissolved, accompanied by the emulsification with a high-speed shear mixing at an optimum velocity. Our preliminary experiment suggested that too rapid addition induced many visible oil droplets separating from the bulk, which might be due to the incomplete dispersion of the oil into the aqueous phase. Also, too slow addition needed more time for high-speed shearing, which produced more extra heat, causing more rapid Brownian motion and leading to aggregation of the emulsion particles. To disperse the oil phase in the water phase sufficiently and avoid producing extra heat, the oil phase should be added to the aqueous phase within 2 min when to prepare a 100-mL BU-LM.

During the high-speed shear mixing process, the interface between the oil phase and the water phase was deformed to an extent to form a stable and homogeneous emulsion by breaking large liquid drops into smaller drops. The most significant method to decrease the drop diameter depended on the high-shearing intensity and the mixing time. Verbich et al. [22] reported that the radii of the droplets in the emulsion decreased with increasing stirring speed and emulsifying time. On one hand, the lowest speed of high-speed shearing mixer was 6000 rpm, insufficient for emulsion system because the appearance of the mixture could not become uniform even mixed for a long time, whereas a shearing speed higher than 10 000 rpm was not required since it caused energy consumption and easily led to emulsion breaking away from the oil-water interface. On the other hand, we controlled the high-speed shear mixing process for 4, 8, 12, and16 min respectively, with a 3-min high-speed shear mixing-on period and a 1-min-off period to optimize the mixing time. The obtained coarse emulsion was directly observed by microscope without dilution. The results exhibited that the number of the large droplets exceeding 5 μm per microscopic field decreased rapidly in the first minutes and then reached a plateau after 12 min. It was reported that the emulsifier became more effective with increasing mixing time, but too long mixing time could cause the emulsifier to drop out from the oil-water interface and as a result of this, the effectiveness of emulsifier decreased, leading to an instability of the emulsion [23]. Therefore, high-speed shear mixing with a shearing speed 10 000 rpm for 12 min including a 3-min rest period was selected to prepare the coarse emulsion "dispersion".

3.2.2 Homogenization pressure and cycles

Once the coarse emulsion was formed, it was necessary to reduce the globule size by homogenization because the coarse emulsion was unstable when placed at the RT. A two-stage high-pressure homogenization, combining procession of shear, turbulence and cavitation forces that could result in the energy-efficient production of consistently fine droplets with a narrow size distribution of approximately 40–200 nm, was used extensively to prepare emulsions. It had been reported that the most important homogenization parameters for controlling droplet size were homogenization pressure, number of cycles and temperature [24, 25]. An ice-water bath was used to avoid producing extra heat that could disrupt droplets over-processed and keep the temperature about 30°C during the homogenization process. Besides, seven different homogenization pressures and twelve homogenization cycles were involved to investigate and optimize the homogenization condition. As shown in Fig. 2A, the mean particle size and SD values reduced as the homogenization pressure increased from 400 to 800 bar, but above 800 bar, the values almost did not change and had a slight increase now and then. Likewise, when the homogenization cycle was up to eight, excess cycles did not obviously decrease the mean particle size and SD values anymore (Fig. 2B). This was because when homogenization pressure and cycles increased to a certain extent, the forces of hole force, shear force and collision force between particles were enhanced, resulting in too much energy in the system and producing some very limited coalescence, which led to an increase in the PSD [26]. Consequently, 800 bar for 8 cycles was chosen as the optimum homogenization parameters.

3.2.3 Temperature

The temperature was another important factor to form a stable emulsion. On one hand, a relative high temperature was needed to dissolve phospholipids and drugs sufficiently. It had been reported that a relatively stable emulsion with smaller particle size could be prepared only if the oil phase and aqueous phase were dissolved at the phospholipids' phase inversion temperature of 70–80°C [27]. Also, a high temperature could decrease the viscosity of the oil phase, leading to a less shearing power to emulsify the oil-water mixture. Therefore, 78 and 70°C were controlled to dissolve or disperse the oil phase and aqueous phase, respectively. On the other hand, a relative low temperature was required during the process of high-pressure homogenization to avoid producing extra heat. Chen and Tao [23] reported that too

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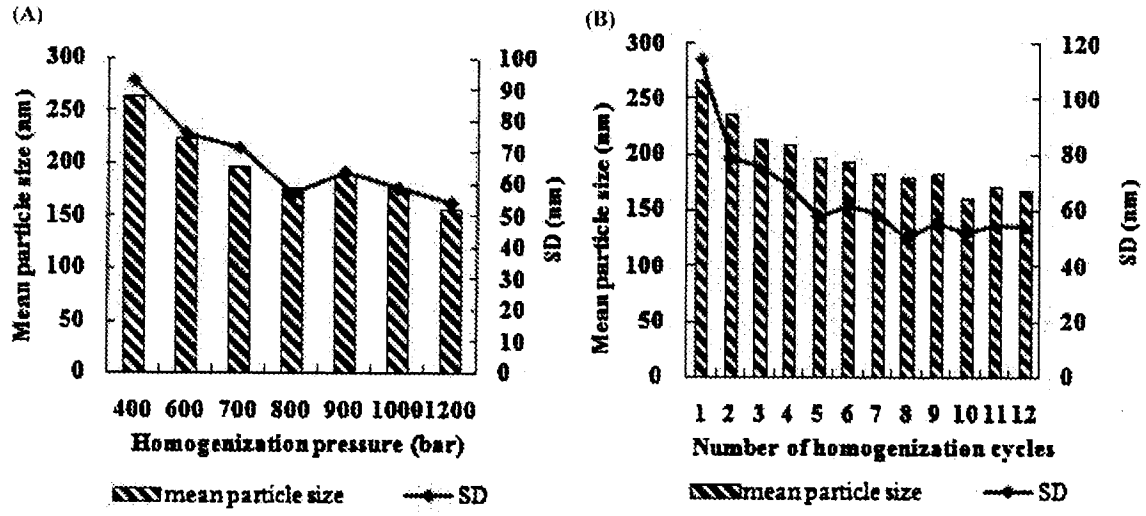


Figure 2. Influence of homogenization pressure (A) and homogenization cycles (B) on PSD of BU-LM.

high temperature would cause more rapid Brownian motion, leading to aggregation of some emulsion particles, and the most stable emulsion was produced at 30 °C. Temperature often had an indirect effect on emulsification as a result of altering the interfacial tension and adsorption of the emulsifier. Usually, the interfacial tension decreased with increasing temperature and a higher temperature was favorable for emulsification. However, an abnormal increase in temperature needed to be avoided because it tended to coagulate the particles, causing a deterioration of the emulsions. In addition, the surfactant, which was loosely adsorbed at the oil-water interface would be separated out from the emulsion to increase the probability of collision and coalescence, thus destabilizing the emulsions. Hence, in our study, ice-water bath was used in the high-pressure homogenization processes to keep the emulsifying temperature at 30°C.

3.2.4 pH

A suitable pH value of intravenous administration of lipid microsphere is from 4.0 to 9.0 since the pH value of human blood is 7.4, and the optimum pH range of the finished emulsion is 6.0–7.0 [28]. Besides, the final pH value of the emulsion should also ensure the slowest degradation of the drug, soybean lecithin, and triglycerides simultaneously. Bufadienolides are easily degradable and catalyzed by acids, bases or enzymes and, C with the most active structures was the most unstable of the three bufadienolides [29]. In the previous study, the detailed degradation processes of B, C, and R in bufadienolides-loaded solution (BU-S) and BU-LM over a range of pH values (4.0–8.0) were investigated. The results demonstrated that the degradation pattern of bufadienolides in BU-LM and BU-S both followed pseudo-first-order kinetics; C was far more unstable than B and R, and the optimum pH value for BU-LM was 6.5 which also minimized the hydrolysis of soybean lecithin; BU-LM could significantly increase the chemical stability of bufadienolides by incorporating the drug into the interior oil phase and the oil-water interfacial film and, C could be protected from degradation to the greatest extent. Consequently, the pH of BU-LM should keep 6.5 before and after sterilization [30].

3.2.5 Thermal sterilization

Sterilization was achieved by autoclaving. It was reported that the thermal sterilization process might be a re-emulsifying procedure or an irreversible redistribution of emulsifier compounds within the oil and aqueous compartments [31]. During the thermal sterilization process, F_0 value, which was used to express the time required to kill a particular organism under specified conditions, should be ensured above 8. Hence, to optimize the thermal sterile conditions, several thermal sterile methods were selected and used, including rotating autoclave in a 115°C water steam bath for 30 min (I), rotating autoclave in a 115°C water steam bath for 45 min (II), rotating autoclave in a 121°C water steam bath for 10 min (III), and rotating autoclave in a 121°C water steam bath for 15 min (IV). Table 6 showed the study results.

According to Table 6, all these sterilization methods provided a good physical appearance without oil droplets or phase separation, demonstrating that the BU-LM could undergo thermal steam autoclaving. However, the results also indicated that longer thermal sterilization could cause hydrolysis of lecithin, produce FFA and cause larger ζ-potential but slower pH value and contents. It is well known that when the sterilization effects are similar, the method with higher sterilization temperature and shorter sterilization time

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Table 6. The effect of different thermal sterilization conditions on the characteristics of BU-LM

Sterilization conditions	PSD (nm)	PI	pH	ζ-Potential (mV)	Physical appearance	Bufadienolide content (%)			EE(%)		
						B	C	R	B	C	R
Before sterilization	175.3 ± 56.6	0.104	6.52	−27.65	Good	21.80	33.12	54.50	86.61	91.88	93.07
Method I	172.3 ± 50.9	0.087	6.43	−26.44	Good	21.61	32.39	53.35	86.24	91.67	93.34
Method II	173.1 ± 56.3	0.106	6.35	−25.21	Good	20.99	32.00	52.60	85.98	91.53	92.87
Method III	169.7 ± 61.4	0.131	6.50	−27.58	Good	21.73	32.99	54.26	86.91	92.08	93.25
Method IV	164.6 ± 57.3	0.121	6.44	−27.14	Good	21.54	32.68	53.71	86.35	91.79	92.89

is better for maintaining the stability of drug on the account of the lower activation energy. Therefore, a 121°C rotating autoclave water steam bath for 10 min was the most suitable thermal method for BU-LM.

3.3 Dilution stability of BU-LM

Injectable drugs often needed to be diluted in clinical application to meet different requirements of the patients. 0.9% sodium chloride injection (NaCl) and 5% glucose injection (Glu) were chosen as the main dilution solvents, because both of them were very commonly used infusion fluids to prevent blood vessel irritation [32]. Lipid microspheres were different from the ordinary injection solutions because of their thermodynamic and dynamic instability, so dilution would play an important role in the stability of LMs. In this study, BU-LM was diluted to 5-fold and 10-fold with 5% Glu or 0.9% NaCl injection to investigate the stability of BU-LM at different time intervals, and the result was shown in Fig. 3.

BU-LM exhibited uniform milky appearance but different PSD after dilution with Glu and NaCl injections. Figure 3A and B showed the mean particle size and SD values of BU-LM after 5-fold or 10-fold dilution with NaCl and Glu injections, respectively. It was worth noticing that after dilution with 5% Glu injection for 4 h, the mean diameter and SD were basically unchanged whatever dilution times, whereas the mean diameter increased gradually and reached a maximum at 4 h, also the SD had an increasing tendency after dilution with 0.9% NaCl injection. All of these indicated that BU-LM was unstable when diluted with 0.9% NaCl injection, which might be due to the high ionic strength of the NaCl solution. The positive charges of Na^+, H^+ and others existed in NaCl injection could be absorbed by the emulsion droplets with negative charges to decrease the ζ-Potential of the emulsion surface, so the electrostatic repulsion between particles decreased and the small particles easily gathered into big particles, leading to the instability of the emulsion in the end. In addition, the positive charges could form electric bridge function between emulsion particles, which was a direct reason for the aggregation of the emulsion droplets. Besides, Fig. 3 displayed that the dilution times almost unaffected the mean diameter and SD under a fixed

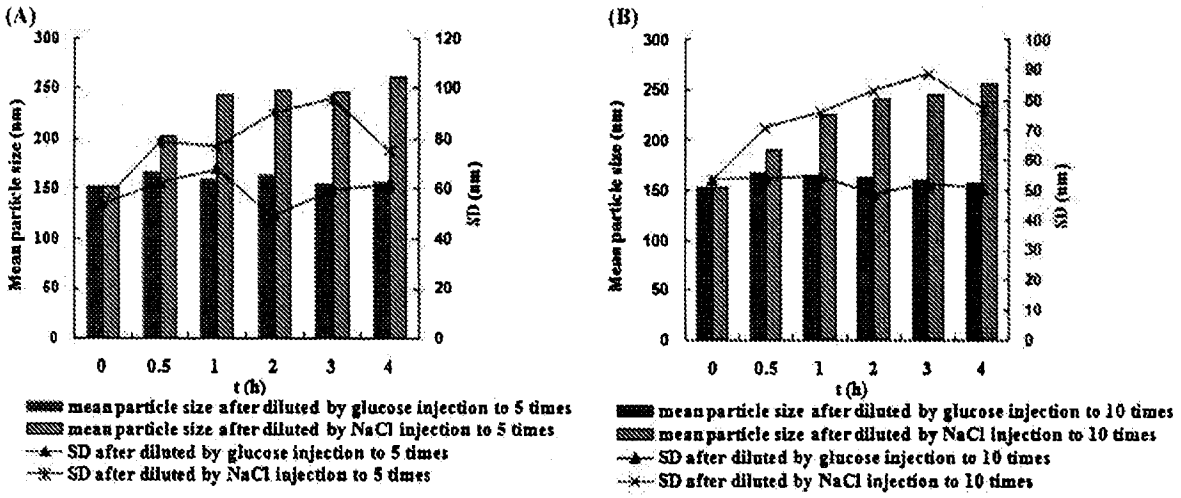


Figure 3. Influence of dilution on PSD of BU-LM.

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Table 7. Characterization of BU-LM after a 121°C rotating steam sterilization for 10 min and storage at 4 ± 2 °C for 18 months (n = 3)

Characterization of BU-LM	Physical appearance	PSD	PI	pH	ζ-Potential (mV)	Bufadienolide content (%)			Sum of the bufadienolide content (%)	EE(%)		
						B	C	R		B	C	R
After autoclaving	Good	175.2 ± 57.3	0.107	6.48 ± 0.02	−32.10 ± 1.04	20.8 ± 0.3	31.3 ± 0.4	50.4 ± 0.4	102.5 ± 0.9	86.9 ± 0.4	91.7 ± 0.5	92.9 ± 0.2
Storage at 4 ± 2°C for 18 months	Good	179.8 ± 59.9	0.111	6.20 ± 0.03	−28.99 ± 1.36	20.3 ± 0.3	30.7 ± 0.2	49.7 ± 0.1	100.7 ± 0.6	86.1 ± 0.5	90.9 ± 0.4	92.1 ± 0.4

dilution medium, for example 5 times or 10 times. It is, therefore, concluded that BU-LM should be diluted with 5% Glu injection, if necessary, to ensure the stability and safety of the emulsion.

3.4 Long-term stability of BU-LM

The long-term stability investigation was carried out for 18 months. The results in Table 7 showed that the parameters which were applied to evaluate the physicochemical stability of BU-LM did not significantly change during 18-month storage at 4 ± 2°C, indicating the excellent physical and chemical stability of BU-LM. Therefore, it could be concluded that BU-LM was an excellent intravenous administration system, which could undergo the real storage conditions for 18 months.

4 Conclusions

In conclusion, a new formulation of intravenous lipid microspheres for bufadienolides was developed in this study to overcome the problems associated with the poor solubility and the chemical instability of bufadienolides. High-speed shear mixing, high-pressure homogenization and thermal sterilization were used for the preparation of BU-LM; PCS, ELS, HPLC, and light microscopy were used for evaluation of BU-LM in vitro by determining essential parameters, such as PSD, ζ-potential, contents and EEs of B, C, and R. The factors influencing the physicochemical stability of BU-LM, such as the oil phase composition and ratio, the type and amount of lecithin, the choice of the co-emulsifier, the addition of osmotic agent, pH, temperature, homogenization and sterilization conditions were discussed thoroughly in this paper. Based on the systematic investigations, the optimum BU-LM was composed of 10% (w/v) MCT, 3.0% (w/v) soybean lecithin, 0.4% (w/v) F68, 0.05% (w/v) sodium oleate, and 2.5% (w/v) glycerol. The oil phase dissolved at 78°C was added slowly to the aqueous phase which was dispersed at 70°C, accompanied by the emulsification with a high-speed shear mixing at 10 000 rpm for 12 min including a 3-min high-speed shear mixing-on period and a 1-min-off period. Then the coarse emulsion was adjusted to pH 6.5, subjected to high-pressure homogenization at 800 bar for 8 cycles at 30°C and sterilized in a 121°C rotating autoclave water steam bath for 10 min. The results obtained proved that BU-LM had a sufficient physicochemical stability after dilution with 5% glucose injection and long-term storage at 4 ± 2°C for 18 months, respectively. Therefore, LM a potentially promising parenteral drug delivery system for bufadienolides.

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References

[1] Kamano, Y., Kotake, A., Hashima, H., Inoue, M. et al., Structure–cytotoxic activity relationship for the toad poison bufadienolides. *Bioorg. Med. Chem.* 1998, *6*, 1103–1115.

[2] Zhao, Y. F., Luo, X. P., Ming, Y. F., Chena, L., Li, Y. M., Rapid separation and determination of resibufogenin and cinobufagin in toad venom and Liushen tablet by β-cyclodextrin modified micellar electrokinetic chromatography. *J. Pharm. Biomed. Anal.* 2006, *41*, 124–128.

[3] Weng, Y., Jin, J., Pan, C., Meng, L., Tang, X., Bioavailability and pharmacokinetics of bufadienolides-loaded lipid microsphere after IV, IP, ID and IG administrations to rats. *Eur. J. Lipid Sci. Technol.* 2011, *113*, 1095–1105.

[4] Venkateswarlu, V., Patlolla, R. R., Lipid microspheres as drug delivery systems. *Ind. J. Pharm. Sci.* 2001, *63*, 450–458.

[5] Muhannud, J., Bernd, W. M., The effect of oil components and homogenization conditions on the physicochemical properties and stability of parenteral fat emulsions. *Int. J. Pharm.* 1998, *163*, 81–89.

[6] Driscoll, D. F., Nehne, J., Peterss, H., Franke, R. et al., The influence of medium-chain triglycerides on the stability of all-in-one formulations. *Int. J. Pharm.* 2002, *240*, 1–10.

[7] Driscoll, D. F., Bacon, M. N., Bistrian, B. R., Physicochemical stability of two different types of intravenous lipid emulsion as total nutrient admixtures. *J. Parenter. Enteral. Nutr.* 2000, *24*, 15–22.

[8] Smyrniotis, V. E., Kostopanagiotou, G. G., Arkadopoulos, N. F. K., Theodoraki, A. et al., Long-chain versus medium-chain lipids in acute pancreatitis complicated by acute respiratory distress syndrome: Effects on pulmonary hemodynamics and gad exchange. *Clin. Nutr.* 2001, *20*, 139–143.

[9] Carpentier, Y. A., Hacquebard, M., Intravenous lipid emulsions to deliver omega 3 fatty acids. *Prostaglandins Leukot. Essent. Fatty Acids.* 2006, *75*, 145–148.

[10] Weingarten, C., Magalhaes, N. S. S., Baszkin, A., Benoita, S., Seiller, M., Interaction of non-ionic ABA copolymer surfactant with phospholipid monolayers: Possible relevance to emulsion stabilization. *Int. J. Pharm.* 1991, *75*, 171–179.

[11] Hansrani, P. K., *Studies on intravenous fat emulsions*, Ph.D. Thesis, University of Nottingham. 1980.

[12] Yamaguchi, T., Nishizaki, K., Itai, S., Hayashi, H., Ohshima, H., Physicochemical characterization of parenteral lipid emulsion: Determination of hamaker constants and activation energy of coalescence. *Pharm. Res.* 1995, *12*, 342–347.

[13] Chansiri, G., Lyons, R. T., Patel, M. V., Hem, S. L., Effect of surface charge on the stability of oil/water emulsions during steam sterilization. *J. Pharm. Sci.* 1999, *88*, 454–458.

[14] Jumaa, M., Müller, B. W., The stabilization of parenteral fat emulsion using non-ionic ABA copolymer surfactant. *Int. J. Pharm.* 1998, *174*, 29–37.

[15] Jumaa, M., Kleinebudde, P., Müller, B. W., Physicochemical properties and hemolytic effect of different lipid emulsion formulations using a mixture of emulsifiers. *Pharm. Acta. Helv.* 1999, *73*, 293–301.

[16] Tadros, T. F., Vincent, B., Encyclopedia of emulsion technology. *P. Becher.* 1983, *1*, 272.

[17] Bahadur, P. S., Riess, G., Block copolymers – A special class of surfactants. *Tenside Surf.* 1991, *28*, 173–179.

[18] Jukes, T. H., Schmidt, C. L. A., The combination of certain fatty acids with lysine, arginine, and salmine. *J. Biol. Chem.* 1935, *110*, 9–17.

[19] Benita, S., Levy, M. Y., Submicron emulsions as colloidal drug carriers for intravenous administration: Comprehensive physicochemical characterization. *J. Pharm. Sci.* 1993, *82*, 1069–1079.

[20] Joseph, T. R., The influence of charged lipids on the flocculation and coalescence of oil-in-water emulsions. I. Kinetic assessment of emulsion stability. *J. Parent. Sci. Technol.* 1990, *44*, 210–215.

[21] Chanana, G. D., Sheth, B. B., Particle size reduction of emulsions by formulation design. I: Effect of polybydroxy alcohols. *J. Parenter. Sci.Technol.* 1993, *47*, 130–134.

[22] Verbich, S. V., Dukhin, S. S., Tarovski, A., Holt, O. et al., Evaluation of stability ratio in oil-in-water emulsion. *Colloids Surfaces A Phys.* 1997, *123–124*, 209–223.

[23] Chen, G., Tao, D., An experimental study of stability of oil–water emulsion. *Fuel Process Technol.* 2005, *86*, 499–508.

[24] Washington, C., Davis, S. S., The production of parenteral feeding emulsions by microfluidizer. *Int. J. Pharm.* 1988, *44*, 169–176.

[25] Bock, T. K., Lucks, J. S., Kleinebudde, P., Mueller, R. H., Mueller, B. W., High pressure homogenisation of parenteral fat emulsions-influence of process parameters on emulsion quality. *Eur. J. Pharm. Biopharm.* 1994, *40*, 157–160.

[26] Akkar, A., Müller, R. H., Intravenous itraconazole emulsions produced by SolEmuls technology. *Eur. J. Pharm. Biopharm.* 2003, *56*, 29–36.

[27] Lu, B., *Drug New Dosage Forms and New Techniques*. People's Medical Publishing House, Beijing 1998, 67–69, 94, 96.

[28] Boberg, J., Hakansson, I., Physical and biological changes in an artificial fat emulsion during storage. *J. Pharm. Pharmacol.* 1964, *16*, 641–646.

[29] Li, F., Yang, R., Weng, Y., Tang, X., Preparation and evaluation of lyophilized liposome-encapsulated bufadienolides. *Drug Dev. Ind. Pharm.* 2009, *35*, 1048–1058.

[30] Weng, Y., Li, F., Chen, W., Miao, Y. Q., Tang, X., Intravenous bufadienolides-loaded lipid microsphere for improving chemical stability. *Eur. J. Lipid Sci. Technol.* 2010, *112*, 1190–1199.

[31] Herman, C. J., Groves, M. J., Hydrolysis kinetics of phospholipids in thermally stressed intravenous lipid emulsion formulations. *J. Pharm. Pharmacol.* 1992, *44*, 539–542.

[32] Wang, J., Cui, Y., Tang, X., Chemical stability of teniposide in aqueous and parenteral lipid emulsions. *Drug Dev. Ind. Pharm.* 2009, *35*, 508–513.

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Preparation of Aprepitant Emulsion for Intravenous Injection

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ABSTRACT: The formulation of aprepitant emulsion for intravenous injection was optimized by single factor test and orthogonal design. The basic properties, such as morphology, particle size, ζ potential and stability of the product were investigated. The results showed that the type and amount of emulsifiers as well as the amount of oleic acid had the greater effect on the stability of the product. The formulation of aprepitant emulsion obtained by optimization was as follows: aprepitant 0.25%, soybean oil 15%, egg yolk lecithin E80 2.5%, and oleic acid 0.125%. The appearance of the product was milky white. The average particle size, PDI, centrifugal stability constant (K_e), ζ potential, pH value, and drug content of the product before and after sterilization were (218.71 ± 1.26) and (220.3 ± 0.53) nm, 0.203 ± 0.016 and 0.210 ± 0.009, 0.21 ± 0.01 and 0.34 ± 0.01, (-37.8 ± 0.2) and (-37.6 ± 0.8) mV, 7.21 ± 0.23 and 7.31 ± 0.30, (101.03 ± 0.89)% and (101.12 ± 1.20)%, respectively.

Key Words: aprepitant; emulsion for injection; preparation; centrifugal stability constant; particle size; ζ potential

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Aprepitant, 1 is the first neurokinin -1(NK-1) receptor blocker which was approved for the market by American FDA in 2003 and was able to block substance P by being combined with NK-1 receptor (mainly exists in the central and peripheral nervous systems). The product is able to pass through blood brain barrier by selectivity and high affinity to receptor NK-1 in brain while low affinity to NK-2 and NK-3 receptors. The product is better than other medicine in reducing nausea and emesis as a result of its low affinity to drug targets (such as dopamine receptor and 5-HT_3 receptor) for treating nausea and emesis induced by chemotherapy. Clinical studies show that 1 is able to effectively prevent acute nausea and emesis induced by chemotherapy, and its unique advantage is to prevent both emesis and delayed emesis in the chemotherapy as well[1].

Officinal emulsion for intravenous injection is one of the hot topics among drug release system research[2]. It can increase the solubility of poorly soluble drug, improve the drug loading of injection, improve the stability of chemically unstable drugs, have sustain-released and efficacy-extended effect, have obvious targeting, and have reduced adverse drug reaction. Therefore, it is appropriate to the industrial production with mature preparation technology and stable product quality[3].

Some vomiting patients are prone to get nausea and emesis when they take drugs orally, which results in invalid drug use[4] because the drugs are vomited and not absorbed. Because the bioavailability of 1 oral preparation is 60%~65% [5], so it is considered to be prepared as intravenous injection to improve curative effect. As 1 is insoluble in water, so it is prepared as emulsion to ensure its solubility.

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1.Instruments and Reagent

Ultraviolet spectrophotometer UV-2450 (Shimadzu company in Japan), high pressure homogenizer AH100D (Seeker industrial company in Canada), laser particle determinator Zetasizer Nano-ZS90 (Malvern company in England), transmission electron microscope JEM-2010 (Japanese electronics firm).

1 Active compound (prepared according to literature[6], 99.4% content, lot number 20110812), soybean oil for injection (Guangzhou Chinese Medicine Modern Traditional Chinese Medicine Research Co., Ltd.), Poloxamer 188 (BASF company in Germany), egg yolk lecithin E80 for injection, oleic acid for injection (Lipoid company in Germany), glycerol (China Medication Group Chemical Reagent Co., Ltd.).

2 Methods and Results

2.1 Preparation of Emulsion

Take appropriate amount of 1, egg yolk lecithin and oleic acid into soybean oil, add appropriate amount of ethanol until completely getting dissolved, and then remove ethanol by pressure reduction in 70 ℃ water bath, in order to give clear oil phase. Under stirring (17,000 r/min), preheat water phase (water for injection, if the prescription includes poloxamer and glycerol, put it into water for injection) to 70 ℃ and then add it slowly into oil phase (8.5:1.5) to give preliminary emulsion. Fill the preliminary emulsion into 2 ml ampoule with nitrogen sealed, after several times act in the high pressure homogenizer, and then sterilize for 15 min under 121 ℃ to give the emulsion.

2.2 Quality Evaluation Index of Emulsion

Morphology: observing the size and distribution of emulsion droplet with transmission electron microscope.

Particle size and ζ potential: assaying the average particle size and ζ potential of emulsion droplet by laser particle determinator (25 ℃ working temperature, water solvent), so evaluate the distribution of emulsion particle and the surface charge of emulsion droplet.

Stability: referring to documentation[7], the centrifugation is adopted to evaluate the stability of preparation. Take appropriate amount of emulsion to centrifuge tube, centrifuge (1000 × *g*) 10 min, take 0.1ml bottom liquid, dilute until 10ml with water, regard the water as the blankness, measure absorbency D at the position of 600 nm. Take 0.1 ml non centrifugal emulsion; use the same method to dilute to measure absorbency D_0. Calculate centrifugal-stability constant (K_e) as following equation. Emulsion is more stable when the value of K_e is less.

$K_e=[(D_0-D)/D]\times 100\%$

In addition, take appropriate amount of emulsion to centrifuge tube, centrifuge (1800×*g*) 1h, take bottom liquid to dilute to certain multiple microscopy with water, check whether crystal occurs, inspect whether the emulsion occurs demulsifying phenomenon.

2.3 Prescription Optimization of Emulsion

2.3.1 Orthogonal Design

Preliminarily it can confirm that the prescription is as below: 10.25%, soybean oil 15%, egg yolk lecithin (*A*) 2%~4%, oleic acid (*B*) 0~0.2%, poloxamer (*C*) 0~0.5%, glycerol (*D*) 0~3% by trial-test and single-factor observation. Continue to observe the effect of factors *A*、*B*、C、D by orthogonal design. The level of each factors refer to Table 1. Prepare 1 emulsion according to the method in "2.1" item method, observe the value of K_e for each set (test results saved in the Editorial department).

Table 1 level table of factors

LEVEL	factor			
	A/%	*B*/%	*C*/%	*D*/%
1	2	0	0	0
2	2.5	0.125	0.2	1.5
3	3	0.15	0.3	2.5
4	4	0.2	0,5	3

Direct analysis and extreme difference analysis show, the best prescription combination is $A_2B_2C_1D_1$, that is, 10 ml preparation contains 0.25 g egg yolk lecithin and 12.5 mg oleic acid, no poloxamer and glycerol are needed. The emulsion made from the prescription shows milky white, is able to slide from the bottle wall after being shaken and it does not stick to the wall.

2.3.2 Single Factor Test

Temperature to emulsify: preheat the oil-water two-phase of prescription optimized above to 50, 60, 70 and 80 ℃ respectively, and thermal mixing to give preliminary emulsion, take out 0.1ml preliminary emulsion after being cooled immediately and dilute to 10ml with water, give D_0 at the position of 600nm. After standing for 24 h at room temperature, take down 0.1ml layer-liquid give D by same method and calculate K_e. The results show that values of K_e for emulsion are 22.54 ± 0.86、17.74 ± 0.40、13.66 ± 0.25、13.63 ± 0.31(n=3) respectively prepared under 50、60、70 and 80 ℃. So the preliminary emulsion is more stable with the increasing of temperature. When over 70 ℃, its stability change is not obvious. Therefore, too high of the temperature will cause the faster oxidation of egg yolk lecithin and oil phase. So the 70 ℃ is chosen as the temperature to emulsify.

Duration to emulsify: mix the oil-water two-phase of prescription optimized at 70 ℃, stir the preliminary emulsions prepared after 1, 3, 6, 10 15 min respectively. After standing 12 h at room temperature, for the preliminary emulsion, layering of the preliminary emulsion emulsified for 1 min is not obvious with longest stable time. But the duration to emulsify does not affect the stability and particle size of final emulsion (refer to Table 2). So the emulsified duration is chosen to be 1 min.

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Table 2 the effect on size of particle of final emulsion and K_e by emulsified duration ($\bar{x} \pm s$, n=3)

Parameter	Emulsified Duration /min				
	1	3	8	10	15
Size of particle/nm	218.63±0.31	218.70±0.26	218.57±0.15	219.03±0.35	219.50±0.20
K_e	0.33±0.01	0.35±0.01	0.33±0.01	0.33±0.01	0.35±0.01

Adding Speed of Water Phase: Add water phase of prescription optimized into oil phase by slow or one-time addition method. Prepare preliminary emulsion according to the method in item "**2.1**", the emulsified duration is 1min, and then stand for 12 h, observe the layering situation of preliminary emulsion to prepare final emulsion. Results show that the layering of preliminary emulsion got by one-time addition method is more obvious than the one got by slow method through visual observation, but the two methods don't affect the stability and the size of particle of final emulsion. The sizes of final emulsion got by the above methods are (219.07 ± 0.76) and (219.40 ± 0.50) nm, K_e are 0.21 ± 0.01 and 0.21 ± 0.01(n=3). So choose the slow addition method to add the water phase to oil phase, and stir and shake synchronously.

Homogeneous Pressure and Homogeneous Frequency Prepare the preliminary emulsion by the prescription optimized and the process, carry out under homogeneous pressure of 300, 400, 500, 600 and 700 bar respectively. The sizes of particle of preparation refer to the Table 3.

Table 3 The effect on Average size of Particle and PDI of Final Emulsion by Homogeneous Pressure and Homogeneous Frequency[1] ($\bar{x}$ ± s, n=3)

Homogeneous Pressure /bar	Homogeneous Frequency						
	1	2	3	4	5	6	7
700	292.40±0.60	259.07±0.59	231.97±0.59	218.13±0.96	228.67±0.68		
	(0.278±0.001)	(0.210±0.002)	(0.183±0.003)	(0.207±0.003)	(0.158±0.003)		
600	266.20±2.61	252.30±2.27	236.00±0.20	222.13±1.37	230.80±3.15	213.50±2.38	
	(0.282±0.005)	(0.130±0.003)	(0.202±0.005)	(0.195±0.009)	(0.157±0.012)	(0.160±0.005)	
500	298.60±2.17	253.37±0.06	233.63±0.38	236.37±0.88	210.50±0.85	229.03±0.90	218.63±0.67
	(0.358±0.005)	(0.210±0.004)	(0.226±0.004)	(0.181±0.003)	(0.209±0.009)	(0.091±0.008)	(0.217±0.003)
400	276.50±1.20	241.73±0.55	223.15±3.53	232.40±1.25	218.73±5.26	223.97±3.95	
	(0.226±0.003)	(0.163±0.005)	(0.203±0.008)	(0.097±0.012)	(0.203±0.016)	(0.146±0.010)	

Remarks: [1] interior and exterior of the brackets are PDI and average size of particle/nm respectively.

Result shows, over 5 times under the homogeneous pressure of 300bar, all of the preparation size of particle only can reach 249.4 nm, which evidences the homogeneous pressure is not enough. Based the results of average size of particle and PDI, choose 5 times under the homogeneous pressure of 400bar, it can be under homogeneous pressures continually.

2.4 Prescription Optimized and Process of 1 Emulsion for Intravenous Injection

By orthogonal design and single-factor observation, it can confirm that prescription optimized and process of 1 emulsion for intravenous injection is as following: take 1 active compound (0.25 %), egg yolk lecithin (2.5 %), oleic acid (0.125 %), and add appropriate amount of ethanol to dissolve, and add soybean oil (15%). And then remove ethanol by pressure reduction in 70 ℃ water bath, in order to give clear oil phase. Add water for injection preheated to 70 ℃ slowly by 1.5:8.5 ratio. Stir (17,000 r/min) for 1 min to give preliminary emulsion, conduct 5 times under the homogeneous pressure of 400bar continually, fill it into 2ml ampoule with nitrogen sealed at 121 ℃ high pressure steam sterilization for 15 min to give it. The average size of particle, PDI, K_e, ζ potential, pH and 1 content (labeled amount%) before and after preparation sterilization are (218.71 ± 1.26), (220.3 ± 0.53) nm, 0.203 ± 0.016, 0.210 ± 0.009, 0.21 ± 0.01, 0.34 ± 0.01, (-37.8 ± 0.2), (-37.6 ± 0.8) mV, 7.21 ± 0.23, 7.31 ± 0.30, (101.03 ± 0.89)% and (101.12 ± 1.20)% (n=3) respectively. Refer Figure 1 and Figure 2 for the distribution of appearance and the size of particle.

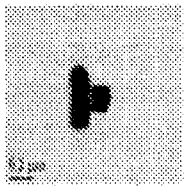


Figure 1

Figure 2

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2.5 Stability Observation

Observe the stability of emulsion after sterilization and 3-month storage after sterilization prepared according to item "**2.4**" method. The results show that no obvious change on the appearance of preparation, still shows milky white, no layering and emulsion demulsifying phenomenon. Refer table 4 for the results of quality evaluation.

Table 4 Observation results of quality evaluation and stability of prescription optimized ($\bar{x}\pm s$, n=3)

Condition	Size of particle/nm	PDI	ζ	Appearance	pH	Content (based on 1)/%
After sterilization	220.3±0.25	0.230±0.006	0.438±0.013	milky white	7.12±0.10	101.32±1.20
3-month storage in room temperature	218.1±0.22	0.235±0.006	0.436±0.015	milky white	7.08±0.12	100.69±0.78
3-month storage in 4 ℃	220.6±0.20	0.230±0.010	0.437±0.012	milky white	6.85±0.10	100.31±0.66

3. Discussion

3.1 Choose the Phospholipin type

Observe the stability of preliminary emulsion prepared with different phospholipin (granulesten, egg yolk lecithin E80 and egg yolk lecithin EPCS) after standing 4 h. The result shows, the layer presents in the preliminary emulsion prepared with granulesten, egg yolk lecithin EPCS, the former shows yellow under high temperature sterilizing. While the layering phenomenon doesn't occur in the preliminary emulsion prepared with egg yolk ecithin E80 under high temperature sterilizing, and its color doesn't change too. The ζ potential of emulsion prepared with egg yolk lecithin EPCS is about -29 mV, which go against to the stability of emulsion. So egg yolk lecithin E80 is chosen.

Some reports compare the emulsification effect and comprehensive quality index among the products with 98%、80%and 30% lecithin. The results show both higher or lower purity of lecithin goes against the shape and stability of fat emulsion. Only the fat emulsion with 80% lecithin is the most stable one. This kind of lecithin contains small amount of acidic lipids, can increase the surface charge of emulsion droplet, so as to be helpful to make the emulsion more stable. However, the phosphatide product containing 95%-100% phosphatidylcholine or phosphatidyl ethanolamine after father purification, it contains almost none of acid lips with less surface charge and lower stability for the emulsion particle after being emulsified. So it is not the ideal emulsion [8]. So the lecithin E80 with 80% content is chosen for trail test.

Phosphatide generally can facilitate to dissolve in this prescription as emulsion. 1 is able to dissolve in alcohol, but not water soluble. When prepare oil phase, only mix the 1 of prescription and the oil phase, add ethanol to dissolve, reduce the pressure, remove the alcohol, but can't obtain the clear oil phase. It is essential to add phosphatide to obtain clear oil phase, so egg yolk lecithin act an assistant role to the dissolving effect.

3.2 Utilization of oleic acid

As egg yolk lecithin contains less amount of lysophosphatide, which can't play a positive effect on some emulsification for drugs. But the oleic acid is able to work as a co-emulsifier. The addition of oleic acid can increase the stiffness of emulsion film, as well as increase the surface charge of emulsion, enhance the dispersion and reduce the aggregation function, easily obtain emulsion with smaller size of particle, enhance the stability of emulsion. The dosage of oleic acid is 2.5% to 5% of the ones of phosphatide. The optimal dosage of oleic acid is 5% of the ones of phosphatide in this prescription.

3.3 Notes in this trail test

When determine the stability of emulsion by centrifugation, should take the sample at the bottom of centrifuge tube with parallel operation each time, because the sample point can affect the results greatly. So in this say, it can avoid the affect caused by different sample point.

Since 1 is not water soluble, once demulsifying phenomenon of emulsion occurs, drug will leak from oil phase to water to produce crystal. So it is useful to determine whether demulsifying phenomenon occurs by crystal.

References:

[1] [illegible]. 2006, 15(3): 238-239.

[2] [illegible]. 2004, 35(9): 552-561.

[3] [illegible]. 2010, 19(16): 1415-1421.

[4] [illegible]. 2010, (10): 59.

[5] [illegible]. 2006, 27(8): 480-484.

[6] [illegible]. 2009, 40(12): 951-953.

[7] [illegible]. 1版. 北京: 人民卫生出版社, 1988: 24.

[8] Washington C. Stability of lipid emulsions for drug delivery[J]. *Adv Drug Deliv Rev*, 1996, 20(2-3): 131-145.

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