PTO/AIA/15 (03-13)
Approved for use through 01/31/2014. 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 displays a valid OMB control number

UTILITY PATENT APPLICATION TRANSMITTAL

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

Attorney Docket No.	244168.000015US6
First Named Inventor	Fabio TRENTO
Title	COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSE
Express Mail Label No.	

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* 36] 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* 5]
6. **Inventor's Oath or Declaration** [*Total Pages* 5] *(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:
      i. ☐ CD-ROM or CD-R (2 copies); or
      ii. ☐ Paper
   c. ☐ Statements verifying identity of above copies

ADDRESS TO: **Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450**

ACCOMPANYING APPLICATION PAPERS

10. ☐ **Assignment Papers** (cover sheet & document(s)) Name of Assignee _____
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:** _____

*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).

19. CORRESPONDENCE ADDRESS

☑ The address associated with Customer Number: 06980 **OR** ☐ Correspondence address below

Name					
Address					
City		State		Zip Code	
Country		Telephone		Email	

Signature	/Clark G. Sullivan/	Date	January 21, 2016
Name (Print/Type)	Clark G. Sullivan	Registration No. (Attorney/Agent)	36,942

This collection of information is required by 37 CFR 1.53(b). 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 12 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.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

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. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
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.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

PTO/AIA/14 (11-15)
Approved for use through 04/30/2017. 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	244168.000015US6
	Application Number	
Title of Invention	COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING	

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
	Fabio		TRENTO	

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

City	Pare, Como	Country of Residence [i]	IT

Mailing Address of Inventor:

Address 1	Via Alla Valle 20B
Address 2	
City	Pare, Como
State/Province	
Postal Code	I-220220
Country [i]	IT

Inventor 2 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Sergio		CANTOREGGI	

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

City	Cagiallo	Country of Residence [i]	CH

Mailing Address of Inventor:

Address 1	Via Sarone 21A
Address 2	
City	Cagiallo
State/Province	
Postal Code	CH-6955
Country [i]	CH

Inventor 3 Remove

Legal Name

PTO/AIA/14 (11-15)
Approved for use through 04/30/2017. 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	244168.000015US6
	Application Number	
Title of Invention	COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING	

Prefix	Given Name	Middle Name	Family Name	Suffix
	Giorgia		ROSSI	

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

City	Cernobbio, Como	Country of Residence [i]	IT

Mailing Address of Inventor:

Address 1	Via della Liberta, 1A		
Address 2			
City	Cernobbio, Como	State/Province	
Postal Code	I-22012	Country [i]	IT

Inventor 4 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Roberta		CANNELLA	

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

City	Varese	Country of Residence [i]	IT

Mailing Address of Inventor:

Address 1	Via Al Colle, 42		
Address 2			
City	Varese	State/Province	
Postal Code	I-21100	Country [i]	IT

Inventor 5 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Daniele		BONADEO	

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

City	Casalzuigno, Varese	Country of Residence [i]	IT

Mailing Address of Inventor:

Address 1	Via Ronco Capo Caccia, 32		
Address 2			
City	Casalzuigno, Varese	State/Province	
Postal Code	I-21030	Country [i]	IT

PTO/AIA/14 (11-15)
Approved for use through 04/30/2017. 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	244168.000015US6
	Application Number	
Title of Invention	COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING	

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).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	06980		
Email Address	ipservicesnyc@troutmansanders.com	Add Email	Remove Email

Application Information:

Title of the Invention	COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING		
Attorney Docket Number	244168.000015US6	**Small Entity Status Claimed**	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	5	**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.

PTO/AIA/14 (11-15)
Approved for use through 04/30/2017. 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	244168.000015US6
	Application Number	
Title of Invention	COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING	

Please Select One:	● Customer Number	US Patent Practitioner	◯ Limited Recognition (37 CFR 11.9)
Customer Number	06980		

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	14069970	2013-11-01
Prior Application Status	Patented		Remove

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
14069970	Continuation of	13077462	2011-03-31	8623826	2014-01-07

Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
13077462	Continuation of	PCT/IB2010/003106	2010-11-18
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
PCT/IB2010/003106	Claims benefit of provisional	61262470	2009-11-18
Prior Application Status			Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
PCT/IB2010/003106	Claims benefit of provisional	61382709	2010-09-14

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

Foreign Priority Information:

PTO/AIA/14 (11-15)
Approved for use through 04/30/2017. 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	244168.000015US6
	Application Number	
Title of Invention	COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING	

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)

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.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	244168.000015US6
	Application Number	
Title of Invention	COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING	

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.

PTO/AIA/14 (11-15)
Approved for use through 04/30/2017. 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	244168.000015US6
	Application Number	
Title of Invention	COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING	

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1 Remove

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. ☒

Organization Name	Helsinn Healthcare SA		
Mailing Address Information For Applicant:			
Address 1	Via Pian Scairolo 9		
Address 2			
City	Lugano/Pazzallo	**State/Province**	
Country	CH	Postal Code	6912
Phone Number		Fax Number	
Email Address			

Additional Applicant Data may be generated within this form by selecting the Add button. Add

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

PTO/AIA/14 (11-15)
Approved for use through 04/30/2017. 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	244168.000015US6
	Application Number	
Title of Invention	COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING	

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.

Remove

If the Assignee or Non-Applicant Assignee is an Organization check here. ☒

Organization Name	Helsinn Healthcare SA

Mailing Address Information For Assignee including Non-Applicant Assignee:

Address 1	Via Pian Scairolo 9		
Address 2			
City	Lugano/Pazzallo	**State/Province**	
Country i	CH	Postal Code	6912
Phone Number		Fax Number	
Email Address			

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button. Add

Signature:

Remove

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). **However, if this Application Data Sheet is submitted with the INITIAL filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).**

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	/Clark G. Sullivan/			Date (YYYY-MM-DD)	2016-01-20
First Name	Clark	Last Name	Sullivan	Registration Number	36,942

Additional Signature may be generated within this form by selecting the Add button. Add

PTO/AIA/14 (11-15)
Approved for use through 04/30/2017. 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	244168.000015US6
	Application Number	
Title of Invention	COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING	

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.**

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. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1 The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3 A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent CooperationTreaty.

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.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Docket No.: 244168.000015US6
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Fabio TRENTO et al.	Customer No.: 06980
Application No.: Submitted herewith (Continuation of U.S. Application No. 14/069,970)	Confirmation No.: Not Yet Assigned
Filing Date: Submitted herewith	Art Unit: Not Yet Assigned
For: COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING	Examiner: Not Yet Assigned

PRELIMINARY AMENDMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

INTRODUCTORY COMMENTS

Prior to examination on the merits, please amend the above-identified U.S. Patent Application as follows.

Amendments to the Specification begin on page 2 of this paper.

Amendments to the Claims begin on page 3 of this paper.

Remarks begin on page 5 of this paper.

AMENDMENTS TO THE SPECIFICATION

A marked-up specification and a substitute specification are submitted herewith. Please replace the specification with the clean copy of the substitute specification. No new matter has been added by this amendment.

AMENDMENTS TO THE CLAIMS

1.-15. (Cancelled)

16) (Original) A method of treating nausea and vomiting for a period of five consecutive days in a patient in need thereof, comprising administering to said patient netupitant or a pharmaceutically acceptable salt thereof, in a therapeutically effective amount which is effective to treat nausea and vomiting during the acute and delayed phases of emesis, and which enters the systemic circulation, crosses the blood brain barrier and occupies at least 70% of NK_1 receptors in the striatum seventy-two hours after said administration.

17) (Original) The method of claim 16, wherein said netupitant occupies at least 80% of NK_1 receptors in the striatum seventy-two hours after said administration

18) (Currently Amended) The method of claim 16 ~~or 17~~, further comprising: a) administering to said patient on day one a first dose of dexamethasone which is ineffective against nausea and vomiting when administered alone, but effective against nausea and vomiting when administered in combination with said netupitant, wherein said first dose comprises from 50 to 70% of a minimum effective dose when administered alone; and b) if said patient is subject to highly emetogenic chemotherapy, administering to said patient, on days two, three and four, a second dose of dexamethasone which is ineffective against nausea and vomiting when administered alone, but effective against nausea and vomiting when administered in combination with said netupitant, wherein said second dose comprises from 40 to 60% of a minimum effective dose when administered alone.

19) (Cancelled)

20) (Cancelled)

21) (Currently Amended) The method of claim 16 ~~any one of claims 16-20,~~ wherein: a) only one dose of netupitant is administered during said five days on day one, comprising about 300 mg. of netupitant as the free base; and b) administering about 12 mg. of dexamethasone on day one; and c) if said patient is undergoing highly emetogenic chemotherapy, administering about 8 mg. of dexamethasone on days two, three and four.

22) (Cancelled)

23) (Currently Amended) The method of claim 16 ~~any one of claims 1-22,~~ wherein said nausea and vomiting is chemotherapy induced nausea and vomiting ("CINV"), radiation

therapy induced nausea and vomiting ("RINV"), or post-operative nausea and vomiting ("PONV").

24) (Currently Amended) The method of claim 16 ~~any one of claims 1-22,~~ wherein said nausea and vomiting is induced by moderately or highly emetogenic chemotherapy.

25) (Currently Amended) The method of claim 16 ~~any one of claims 1-24,~~ comprising administering moderately or highly emetogenic chemotherapy within from about one hour to about two hours of said administration of said netupitant or pharmaceutically acceptable salt thereof.

26) (Currently Amended) The method of claim 16 ~~any one of claims 1-25,~~ comprising treating nausea and vomiting in response to highly emetogenic chemotherapy during the acute phase, or in response to highly emetogenic chemotherapy during the delayed phase, or in response to moderately emetogenic chemotherapy during the acute phase, or in response to moderately emetogenic chemotherapy during the delayed phase.

27.-51. (Cancelled)

52) (New) The method of claim 16, comprising orally administering from about 200 to about 400 mg of netupitant as the free base.

53) (New) The method of claim 16, comprising orally administering about 300 mg of netupitant as the free base.

54) (New) A method of treating nausea and vomiting for a period of five consecutive days in a patient in need thereof, comprising administering to said patient netupitant or a pharmaceutically acceptable salt thereof, in a therapeutically effective amount which is effective to treat nausea and vomiting during the acute and delayed phases of emesis.

55) (New) The method of claim 54, comprising orally administering from about 200 to about 400 mg of netupitant as the free base.

56) (New) The method of claim 54, comprising orally administering about 300 mg of netupitant as the free base.

REMARKS

After the amendment, claims 16-18, 21, 23-26, and 52-56 are pending. Claims 18, 21, 23, 24, 25 and 26 are amended to remove multiple dependencies. Claims 52-56 are added to include dose limitations, and are supported on page 13 of the specification. No new matter is added by the amendment.

The specification has been amended to correct the line spacing of the specification to be in compliance with 37 C.F.R. 1.52(b). No new matter is added by this amendment.

Early and favorable examination is requested.

The Commissioner is authorized to charge any deficiency or credit any excess in this fee to Deposit Account No. 20-1507 of Customer No. 06980.

Dated: January 21, 2016

Respectfully submitted,

/Clark G. Sullivan/

Clark G. Sullivan
Registration No.: 36,942
Troutman Sanders LLP
875 Third Avenue
New York, New York 100022
Direct Tel: (212) 704-6105
Fax: (212) 704-6288
Direct E-mail:
clark.sullivan@troutmansanders.com
Attorneys/Agents for Applicant

NONPROVISIONAL APPLICATION FOR UNITED STATES PATENT

for

COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING

by:

Fabio Trento, a citizen of Italy residing at Via Alla Valle 20B I-22020 Parè (Como - Italy); Sergio Cantoreggi, a citizen of Switzerland residing at Via ai Ronchi, 37 CH-6943 Vezia Switzerland; Giorgia Rossi, a citizen of Italy residing at Via della Libertà, 1A - I-22012 Cernobbio (Como - Italy); Roberta Cannella, a citizen of Italy, residing at Via Al Colle, 42 - I-21100 Varese, Italy; Daniele Bonadeo, a citizen of Italy residing at Via Ronco Capo Caccia, 32 - I-21030 Casalzuigno, Varese, Italy

COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims benefit of U.S. Provisional Application No. 61/262,470, filed November 18, 2009; U.S. Provisional Application No. 61/382,709, filed September 14, 2010; and International Patent Application No. PCT/US10/57192, filed November 19, 2010. Application Nos. 61/262,470 and 61/382,709 and PCT Application No. PCT/US10/57192 are hereby incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

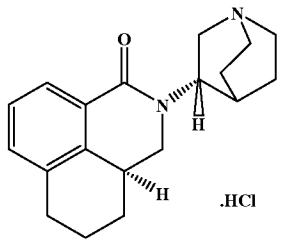
The present invention relates to the use of centrally acting NK_1 antagonists to treat nausea and vomiting, particular nausea and vomiting induced by highly emetogenic chemotherapy, and to the treatment of such nausea and vomiting over multiple consecutive days. The present invention also relates to combined oral dosage forms of palonosetron and netupitant.

BACKGROUND OF THE INVENTION

With the development of the 5-HT_3 antagonist in the early 1990s, there emerged new strategies in the medical community to better control nausea and vomiting caused by various medical procedures, including chemotherapy (CINV), surgery (PONV), and radiation therapy (RINV). When added to steroids such as dexamethasone, several 5-HT_3 antagonists have been demonstrated to significantly improve the standard of life for patients undergoing emetogenic medical procedures. Examples of 5-HT_3 antagonists include ondansetron, marketed by GlaxoSmithKline, and palonosetron, developed by Helsinn Healthcare.

Palonosetron hydrochloride has recently emerged as a highly efficacious anti-nauseant and anti-emetic agent. See PCT publications WO 2004/045615 and 2004/073714 from Helsinn Healthcare. Palonosetron hydrochloride is sold in the United States as a sterile injectable liquid under the ALOXI® brand, in sterile unit dose vials containing 0.075 or 0.25 mg. of palonosetron hydrochloride. Palonosetron hydrochloride also is also sold as an orally administered soft-gel dosage form containing 0.5 mg. of palonosetron hydrochloride.

The official chemical name for palonosetron hydrochloride is (3aS)-2-[(S)-l-Azabicyclo [2.2.2]oct-3-yl]- 2,3,3a,4,5,6-hexahydro-l-oxo-l*H*beriz[*de*] isoquinoline hydrochloride (CAS No. 119904-90-4); its empirical formula is $C_{19}H_{24}N_2O{\cdot}HCl$, and its molecular weight is 332.87. The compound is represented by the following chemical structure:

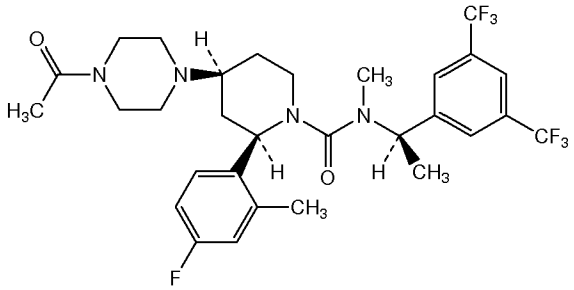


Methods of synthesizing palonosetron are described in U.S. Patent Nos. 5,202,333 and 5,510,486. Pharmaceutically acceptably dosage forms are described in PCT publications WO 2004/067005 and WO 2008/049552 from Helsinn Healthcare.

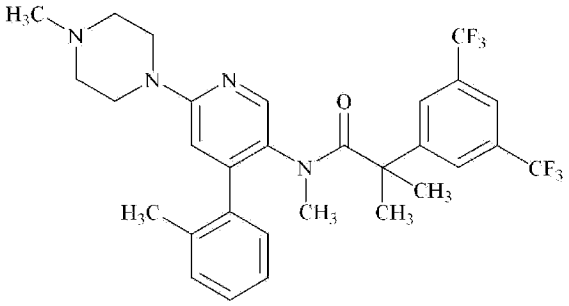
NK_1 antagonists have also recently emerged as a tool for combating nausea and vomiting from emetogenic medical procedures. Most recently, aprepitant was approved by the Food and Drug Administration ("FDA") for use in combination with other anti-emetic agents for the prevention of nausea and vomiting from moderately and highly emetogenic chemotherapy. However, it quickly became apparent that aprepitant's effect was limited principally to vomiting – not nausea – and that aprepitant did not provide as much benefit during the acute phase of CINV. When tested against nausea in humans, aprepitant was unable to induce a significant reduction in the incidence or severity of nausea following moderately or highly emetogenic chemotherapy when compared to a $5\text{-}HT_3$ antagonist alone. See FDA Approved Labeling for Emend®. Thus, while aprepitant is approved by FDA for the prevention of nausea and vomiting in humans, this indication is somewhat misleading because aprepitant did not reduce nausea in the clinical trials preformed for aprepitant more than nausea controlled by the other components of the anti-emetic regimen. In addition, the results reported in Grunberg *et al.*, SUPPORT CANCER CARE (2009) 17:589-594, from a combined treatment of aprepitant and palonosetron, were far from promising.

Merck & Co. markets aprepitant, as EMEND® in the United States. The product is approved in a capsule dosage form, and is marketed for the prevention of CINV (acute and delayed) in combination with other anti-emetic agents such as ondansetron and metoclopramide. The product reportedly has a terminal half-life of from 9 to 13 hours. While aprepitant has

demonstrated some effect against nausea, its effects have been inconsistent. Casopitant is another NK_1 antagonist that has been tested against nausea and vomiting in humans. A clinical study of casopitant is discussed in *Therapeutics and Clinical Risk Management* 2009:5 pp375-384 to Ruhlmann et al. and *Drug Metabolism and Disposition*, vol.37, No. 8, 2009, pp.1635-1645 to Pellegatti et al. As reported by Ruhlmann *et al.* in THERAPEUTICS AND CLINICAL RISK MANAGEMENT, 2009:5 375-384, casopitant had no statistically significant effect against nausea when administered in response to moderately emetogenic chemotherapy, and even induced nausea as a side effect. Casopitant has the formula (2*R*,4*S*)-4-(4-acetytlpiperazin-1-yl)-*N*-{(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethyl}-2-(4-fluoro-2-methylphenyl)-*N*-methylpiperidine-1-carboxamide, and the below chemical structure:



Netupitant is another selective NK_1 receptor antagonist under development by Helsinn Healthcare, having the formula 2-[3,5-bis(trifluoromethyl)phenyl]-N,2-dimethyl-N-[4-(2-methylphenyl)-6-(4-methylpiperazin-1-yl)pyridin-3-yl]propanamide, or Benzeneacetamide, N,α,α-trimethyl-N-[4-(2-methylphenyl)-6-(4-methyl-1-piperazinyl)-3-pyridinyl]-3,5-bis(trifluoromethyl)-, and the below chemical structure:



Methods of synthesizing and formulating netupitant and its prodrugs are described in U.S. Patent Nos. 6,297,375, 6,719,996 and 6,593,472 to Hoffmann La Roche.

Other representative NK_1 antagonists include ZD4974 (developed by AstraZeneca), CGP49823 (developed by Ciba-Geigy), Lanepitant and LY686017 (developed by Eli Lilly),

FK888 (developed by Fujisawa), Vofopitant, Vestipitant and Orvepitant (developed by GlaxoSmithKline), Befetupitant (developed by Hoffmann-La Roche), R116031 (developed by Janssen), L-733060 and L-736281 (developed by Merck), TKA731, NKP608 and DNK333 (developed by Novartis), CP-96345, CP-99994, CP-122721, CJ-17493, CJ-11974 and CJ-11972 (developed by Pfizer), RP67580 and Dapitant (developed by Rhone-Poulenc Rorer), Nolpitantium and SSR240600 (developed by Sanofi-Aventis), SCH388714 and Rolapitant (developed by Schering-Plough), TAK637 (developed by Takeda), HSP117 (developed by Hisamitsu), KRP103 (developed by Kyorin Pharm) and SLV317 (developed by Solvay). Chemical structures of the above-mentioned NK_1 antagonists are shown below and discussion of those compounds as well as other NK_1 antagonists is present in *Expert Opin. Ther. Patents* (2010) 20(8), pp1019-1045 by Huang et al.

The background of U.S. Patent No. 6,297,375 suggests that NK_1 antagonists are useful for treating a variety of conditions in which substance P (the natural ligand for the NK_1 receptor) is active. These conditions include depression, pain (especially pain resulting from inflammatory conditions such as migraine, rheumatoid arthritis, asthma, and inflammatory bowel disease), central nervous system (CNS) disorders such as Parkinson's disease and Alzheimer's disease, headache, anxiety, multiple sclerosis, attenuation of morphine withdrawal, cardiovascular changes, oedema, chronic inflammatory diseases such as rheumatoid arthritis, asthma/bronchial hyperreactivity and other respiratory diseases including allergic rhinitis, inflammatory diseases of the gut including ulcerative colitis and Crohn's disease, ocular injury and ocular inflammatory diseases. The background even mentions motion sickness and vomiting, but fails to call out nausea specifically.

Accordingly, there is a need in the art for more effective treatments of nausea and vomiting, particularly nausea and vomiting emanating from chemotherapy, radiotherapy and surgery. In addition, given the prolonged incidence of nausea and vomiting induced by these emetic events, there is a need for treating such nausea and vomiting for a prolonged period of time. Further, there is a need for the development of dosage forms to reduce drug-drug interaction, improve stability, and potentiate effects of each component of the combined dosage forms.

OBJECTS OF THE INVENTION

Accordingly, it is an object of the invention to provide new methods for treating or preventing nausea and vomiting using an NK_1 antagonist, particularly netupitant.

It is another object of the invention to provide methods for treating or preventing nausea and vomiting in patients undergoing chemotherapy, radiotherapy, or surgery.

Still another object of the invention is to augment existing treatments for CINV, RINV or PONV by steroids and 5-HT_3 antagonists, and thereby provide additional protection against both nausea and vomiting, especially during the acute and delayed phases.

Another object of the invention is to provide a single combined dose of netupitant and a 5-HT_3 antagonist and to the use of that single dose without further dosing, for the treatment of nausea and vomiting during the acute and delayed phases of CINV, RINV or PONV.

It is another object to provide novel methods to treat nausea, vomiting, and other undesirable effects from moderately emetogenic and highly emetogenic chemotherapy ("MEC and HEC"), especially HEC, during the acute and delayed phases following such treatments.

It is another object to provide novel dosage forms to reduce drug-drug interaction, improve stability, enhance bioavailability and potentiate therapeutic effect of each component of the combined dosage forms comprising netupitant and/or 5-HT_3 antagonist and/or dexamethasone, in treating or preventing nausea and vomiting.

SUMMARY OF THE INVENTION

After extensive testing into the clinical effects of netupitant, it has unexpectedly been discovered that netupitant is active against nausea, and that a single dose of netupitant is able to treat nausea and vomiting in response to highly and moderately emetogenic chemotherapy for five consecutive days. It has also been discovered, quite unexpectedly, that netupitant exhibits unique binding habits to NK_1 receptors in the brain. In particular, it has been discovered that netupitant binds to NK_1 receptors in the striatum in a long-lasting manner, and that less than 20 or 30% of netupitant is released from striatum NK_1 receptors even ninety-six hours after administration. This is in stark contrast to aprepitant, in which receptor binding drops swiftly over time, and must be dosed repeatedly if emesis control is desired throughout the delayed phase; and which shows no meaningful effect against nausea.

These discoveries have led to the development of a unique dosing regimen to treat nausea during the first day after an emesis-inducing event, in addition to the second, third, fourth and fifth days after such induction. Therefore, in one embodiment the invention provides a method of treating nausea and vomiting for a period of five consecutive days in a patient in need thereof, comprising administering to said patient netupitant or a pharmaceutically acceptable salt thereof in an amount which is therapeutically effective against nausea and vomiting during the acute and delayed phases, and which is effective to enter the systemic circulation, cross the blood brain barrier and occupy at least 70% of NK_1 receptors in the striatum seventy-two hours after said administration.

In another embodiment, the netupitant is combined with other anti-emetic agents, including a 5-HT_3 antagonist such as palonosetron and a corticosteroid such as dexamethasone, in a manner that results in even greater efficacy against nausea. It has been discovered that palonosetron is much more effective in combinations with netupitant than it is in combination with aprepitant, as reported by Grunberg et al., Support Cancer Care (2009) 17:589-594. In addition, palonosetron shows an improved pharmacokinetic profile (e.g., better bioavailability) when palonosetron is in combination with netupitant as opposed to palonosetron in single dose administration. Based on these discoveries, solid oral dosage forms have been developed that combine netupitant or another NK1 antagonist and palonosetron for the treatment of acute and delayed emesis.

It has also been discovered that netupitant potentiates the effect of dexamethasone, such that the dexamethasone is effective even when administered at sub-therapeutic doses (i.e. doses at which the dexamethasone would be ineffective if administered by itself). Therefore, in another embodiment the invention provides a combination therapy for treating nausea and vomiting for five consecutive days in a patient in need thereof, consisting essentially of:

- Day 1 netupitant -- administering to said patient on day one netupinant or a pharmaceutically acceptable salt thereof, in an amount which is therapeutically effective against nausea and vomiting during the acute and delayed phases, and which is effective to enter the systemic circulation, cross the blood brain barrier and occupy at least 70% of NK_1 receptors in the striatum seventy-two hours after said administration;
- Day 1 palonosetron -- administering to said patient on day one a therapeutically effective amount of a 5-HT_3 antagonist (preferably palonosetron) effective to treat said nausea and vomiting during the acute and delayed phases;

- Day 1 dexamethasone -- administering to said patient on day one a first dose of dexamethasone which is ineffective against nausea and vomiting when administered alone, but effective against nausea and vomiting when administered in combination with said netupitant and palonosetron, wherein said first dose comprises from 50 to 70% of a minimum effective dose when administered alone; and
- Days 2-5 dexamethasone – when the patient is undergoing highly emetogenic chemotherapy, administering to said patient, on days two, three and four, a second dose of dexamethasone which is ineffective against nausea and vomiting when administered alone, but effective against nausea and vomiting when administered in combination with said netupitant, wherein said second dose comprises from 40 to 60% of a minimum effective dose when administered alone on days two, three and four.

The dosage forms are extremely versatile and stable owing to their unique design and formulation. This versatility and stability is accomplished by formulating the NK1 antagonist and palonosetron in separate dosage forms and combining the dosage forms in one capsule. Thus, for example, the palonosetron can be formulated in a small gel-cap at a dose of around 0.5 mg, and the netupitant or other NK1 antagonist formulated in a tablet at a dose of about 100 to 150 mg. A capsule can then be filled with one or more palonosetron gel-caps and one or more netupitant (or other NK1 antagonist) tablets, depending on the therapeutic objective for the product. Because the palonosetron and NK1 antagonist are in separate dosage units, they can be formulated without regard to the stability of the other, and without degradation to by-products, for instance (3S)-3-[(3aS)-1-oxo- 2,3,3a,4,5,6-hexahydro-1*H*-benzo[*de*] isoquinoline-2-yl]-1-azoniabicyclo[2.2.2]octan-1-olate, a degradation by-product of palonosetron. As a result, the presently discovered dosage forms offer advantages, such as, reducing drug-drug interaction, improving stability, and potentiating effects of each component of the dosage forms in treating or preventing emesis.

Thus, in one embodiment the invention provides an orally administered dosage form comprising a combination of palonosetron and an NK1 antagonist (preferably netupitant), or a pharmaceutically acceptable salt or prodrug thereof.

In another embodiment the invention provides an orally administered capsule dosage form comprising (a) an outer shell; (b) one or more tablets housed within said outer shell, each comprising an NK1 antagonist (preferably netupitant) or a pharmaceutically acceptable salt or prodrug thereof and one or more pharmaceutically acceptable excipients; and (c) one or more soft-gel capsules housed within the outer shell, each comprising palonosetron or a pharmaceutically acceptable ester or prodrug thereof and one or more pharmaceutically

acceptable excipients; wherein said dosage form comprises (3S)-3-[(3aS)-1-oxo- 2,3,3a,4,5,6-hexahydro-1*H*-benzo[*de*] isoquinoline-2-yl]-1-azoniabicyclo[2.2.2]octan-1-olate in an amount that does not exceed 3 wt.%.

In still other embodiments the invention provides methods of treating acute and delayed-onset emesis by administering the dosage forms of the present invention to a human in need thereof, preferably shortly before the emesis inducing event.

Additional embodiments and advantages of the invention will be set forth in part in the description which follows, and in part will be obvious from the description, or may be learned by practice of the invention. The embodiments and advantages of the invention will be realized and attained by means of the elements and combinations particularly pointed out in the appended claims. It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as claimed.

BRIEF DESCRIPTION OF THE DRAWINGS

The accompanying drawings, which are incorporated in and constitute a part of this specification, illustrate several embodiments of the invention and together with the description, serve to explain the principles of the invention.

FIG. 1 depicts a capsule containing one soft-gel capsule of palonosetron and three tablets of netupitant.

FIG. 2 is a two dimensional graph plotting the pharmacokinetic profile of netupitant in humans following oral administration of netupitant alone and netupitant together with palonosetron.

FIG. 3 is a two dimensional graph plotting the pharmacokinetic profile of palonosetron in humans following oral administration of palonosetron alone and palonosetron together with netupitant.

FIG. 4 is a two dimensional graph plotting mean plasma concentrations of dexamethasone over time following administration with and without netupitant.

FIG. 5 contains two bar graphs that depict the average NK_1 receptor occupancy at 6, 24, 48, 72 and 96 hours after a single oral dose of 100, 300 and 450 mg. netupitant (N=2 for each dose) in striatum and occipital cortex, as measured using positron emission topography.

DETAILED DESCRIPTION OF THE INVENTION

The present invention may be understood more readily by reference to the following definitions and detailed description of preferred embodiments of the invention and the non-limiting Examples included therein.

Definitions and Use of Terms

When the singular forms "a," "an" and "the" or like terms are used herein, they will be understood to include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a pharmaceutical carrier" includes mixtures of two or more such carriers, and the like. The word "or" or like terms as used herein means any one member of a particular list and also includes any combination of members of that list.

When used herein the term "about" or "ca." will compensate for variability allowed for in the pharmaceutical industry and inherent in pharmaceutical products, such as differences in product strength and bioavailability due to manufacturing variations and time-induced product degradation. The term allows for any variation which in the practice of pharmaceuticals would allow the product being evaluated to be considered pharmaceutically equivalent or bioequivalent, or both if the context requires, to the recited strength of a claimed product.

Throughout the description and claims of this specification, the word "comprise" and variations of the word, such as "comprising" and "comprises," means "including but not limited to," and is not intended to exclude, for example, other additives, components, integers or steps.

As used herein, the term "Pharmaceutically acceptable" means that which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes that which is acceptable for veterinary use as well as human pharmaceutical use. In addition, the term "pharmaceutically acceptable salt" refers to a salt of a compound to be administered prepared from pharmaceutically acceptable non-toxic acids. Examples of suitable inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, sulfuric, and phosphoric. Suitable organic acids may be selected from aliphatic, aromatic, carboxylic and sulfonic classes of organic acids, examples of which are formic, acetic, propionic, succinic, camphorsulfonic, citric, fumaric, gluconic, isethionic, lactic, malic, mucic, tartaric, para-toluenesulfonic, glycolic, glucuronic, maleic, furoic, glutamic, benzoic, anthranilic,

salicylic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, pantothenic, benzenesulfonic (besylate), stearic, sulfanilic, alginic, galacturonic, and the like.

Pharmaceutically acceptable salts of palonosetron include palonosetron hydrochloride. Pharmaceutically acceptable pro-drugs of netupitant include those described in U.S. Patent Nos. 6,593,472, 6,747,026 and 6,806,370, including the N-oxide of netupitant. The contents of these publications are incorporated herein by reference. When a molecule is referred to herein in its base or salt form, it will be understand also to encompass other pharmaceutically acceptable salt forms of the molecule.

As used herein, "therapeutically effective amount" refers to an amount sufficient to elicit the desired biological response. The therapeutically effective amount or dose will depend on the age, sex and weight of the patient, and the current medical condition of the patient. The skilled artisan will be able to determine appropriate dosages depending on these and other factors in addition to the present disclosure.

The minimum effective dose of dexamethasone, when used to treat CINV induced by highly emetogenic chemotherapy, has been demonstrated to be 20 mg. administered orally or by injection on day one, and sixteen mg. administered orally or by injection on days two, three and four. Jordan *et al.*, THE ONCOLOGIST, Vol. 12, No. 9, 1143-1150, September 2007. When used to treat CINV induced by moderately emetogenic chemotherapy, the minimum effective dose of dexamethasone is 20 mg. administered orally or by injection on day one, and zero mg. on days two, three and four.

The terms "treating" and "treatment," when used herein, refer to the medical management of a patient with the intent to cure, ameliorate, stabilize, or prevent a disease, pathological condition, or disorder. This term includes active treatment, that is, treatment directed specifically toward the improvement of a disease, pathological condition, or disorder, and also includes causal treatment, that is, treatment directed toward removal of the cause of the associated disease, pathological condition, or disorder. In addition, this term includes palliative treatment, that is, treatment designed for the relief of symptoms rather than the curing of the disease, pathological condition, or disorder; preventative treatment, that is, treatment directed to minimizing or partially or completely inhibiting the development of the associated disease, pathological condition, or disorder; and supportive treatment, that is, treatment employed to

supplement another specific therapy directed toward the improvement of the associated disease, pathological condition, or disorder.

As used herein, the term "significantly" refers to a level of statistical significance. The level of statistical significant can be, for example, of at least $p<0.05$, of at least $p<0.01$, of at least $p<0.005$, or of at least $p<0.001$. Unless otherwise specified, the level of statistical significance is $p<0.05$. When a measurable result or effect is expressed or identified herein, it will be understood that the result or effect is evaluated based upon its statistical significance relative to a baseline. In like manner, when a treatment is described herein, it will be understood that the treatment shows efficacy to a degree of statistical significance.

5-HT_3 antagonists include the various setrons such as, for example, palonosetron, ondansetron, dolasetron, tropisetron, and granisetron, and their pharmaceutically acceptable salts. A preferred 5-HT_3 antagonist is palonosetron, especially its hydrochloride salt.

"Highly emetogenic chemotherapy" refers to chemotherapy having a high degree of emetogenic potential, and includes chemotherapy based on carmustine, cisplatin, cyclophosphamide ≥ 1500 mg/m^2, dacarbazine, dactinomycin, mechlorethamine, and streptozotocin.

"Moderately emetogenic chemotherapy" refers to chemotherapy having a moderate degree of emetogenic potential, and includes chemotherapy based on carboplatin, cyclophosphamide < 1500 mg/m^2, cytarabine > 1 mg/m^2, daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, and oxaliplatin.

Acute emesis refers to the first twenty-four hour period following an emesis-inducing event. Delayed emesis refers to the second, third, fourth and fifth twenty-four hour periods following an emesis-inducing event. When a treatment is said to be effective during the delayed phase, it will be understood to mean that the effectiveness of the treatment is statistically significant during the entire delayed phase, regardless of whether the treatment is effective during any particular twenty-four hour period of the delayed phase. It will also be understood that the method can be defined based upon its effectiveness during any one of the twenty-four hour periods of the delayed phase. Thus, unless otherwise specified, any of the methods of treating nausea and/or vomiting during the delayed phases, as described herein, could also be practiced to treat nausea and/or vomiting during the second, third, fourth or fifth twenty-four hour periods following an emesis inducing event, or an combination thereof.

When ranges are given by specifying the lower end of a range separately from the upper end of the range, it will be understood that the range can be defined by selectively combining any one of the lower end variables with any one of the upper end variables that is mathematically possible.

Methods of Treatment

As noted above, the invention is premised on several unique discoveries, and provides the following independent methods that can be practiced according to the present invention, including:

In a first principal embodiment, the invention provides a method of treating nausea and vomiting for a period of five consecutive days in a patient in need thereof, comprising administering to said patient netupitant or a pharmaceutically acceptable salt thereof in an amount which is therapeutically effective to treat nausea and vomiting during the acute and delayed phases, which enters the systemic circulation, crosses the blood brain barrier and occupies at least 70% of NK_1 receptors in the striatum seventy-two hours after said administration.

In a second principal embodiment, the invention provides a combination therapy for treating nausea and vomiting for five consecutive days in a patient in need thereof, comprising:

(i) administering to said patient on day one netupitant or a pharmaceutically acceptable salt thereof, in an amount which is therapeutically effective to treat nausea and vomiting during the acute and delayed phases, which enters the systemic circulation, crosses the blood brain barrier and occupies at least 70% of NK_1 receptors in the striatum seventy-two hours after said administration;

(ii) administering to said patient on day one a therapeutically effective amount of a 5-HT_3 antagonist (preferably palonosetron, more preferably 0.5 mg. of oral palonosetron as palonosetron hydrochloride) effective to treat said nausea and vomiting during the acute and delayed phases;

(iii) administering to said patient on day one a first dose of dexamethasone which is ineffective against nausea and vomiting when administered alone, but effective against nausea and vomiting when administered in combination with said netupitant and palonosetron, wherein said first dose comprises from 50 to 70% of a minimum effective dose when administered alone; and

(iv) if the patient is undergoing highly emetogenic chemotherapy, administering to said patient, on days two, three and four, a second dose of dexamethasone which is ineffective against nausea and vomiting when administered alone, but effective against nausea and vomiting

when administered in combination with said netupitant, wherein said second dose comprises from 40 to 60% of a minimum effective dose when administered alone on days two, three and four.

Various sub-embodiments are envisaged for these principal embodiments. For example, the netupitant can be administered as a free base or a pharmaceutically acceptable salt thereof, but is preferably administered as the free base. In addition, the netupitant is preferably administered in an amount ranging from about 50 to about 500 mg., from about 200 to about 400 mg., and preferably about 300 mg., based on the weight of the free base. A preferred route of administration for the netupitant is oral. In terms of binding to NK_1 receptors, the netupitant preferably binds to at least 80 or even 85% of NK_1 receptors in the striatum seventy-two hours after administration. As of ninety six hours after administration, the netupitant preferably binds less than 70, 60, 50 or even 40% of said NK_1 receptors.

The methods of the present invention are all effective at treating or preventing nausea and vomiting induced by numerous events, including chemotherapy induced nausea and vomiting ("CINV"), from moderately or highly emetogenic chemotherapy, radiation therapy induced nausea and vomiting ("RINV"), and post-operative nausea and vomiting ("PONV"). The method is preferably performed shortly before the emesis inducing event (i.e. no more than 1 or 2 hours before the event). The methods may be used to treat nausea and vomiting during the acute phase of emesis, or during the delayed phase.

The drugs specified by the individual embodiments may be administered by any suitable dosing regimen, as is well known in the art, but in a preferred embodiment the netupitant, 5-HT_3 antagonist and steroid are administered orally. A preferred oral dose of palonosetron ranges from about 0.075 to about 1.0 mg, or from about 0.25 to about 0.75 mg, but is preferably about 0.5 mg. A preferred oral dose of netupitant ranges from about 50 to 500 mg, or from about 200 to about 400 mg, but is preferably about 300 mg. A preferred dose of corticosteroid, preferably dexamethasone, is 12 mg administered orally or via injection on the first day of treatment, and 8 mg administered orally or via injection on the second, third and fourth days after said treatment.

It will be further understood that the netupitant can be administered in prodrug form, in which case the invention will provide a method of treatment by inducing plasma levels of netupitant, and in each case the plasma level of netupitant induced by the prodrug administration

will correspond to the level attained by the administration of netupitant or its pharmaceutically acceptable salt, in the doses and routes of administration described herein.

Pharmaceutical Compositions

Various pharmaceutical compositions can be developed that make use of the combinations described herein. The composition can be administered by any appropriate route, for example, orally, parenterally, or intravenously, in liquid or solid form.

Preferred modes of administrations of the active compounds are injectable and/or oral. These compositions will generally include an inert diluent or an edible carrier. They may be enclosed in gelatin capsules (for oral use) or compressed into tablets (for oral or buccal use) or formulated into troches (for buccal use). For these purposes, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition.

Tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a gliding such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring. When the dosage unit form is a capsule, it can contain, in addition to material of the above type, a liquid carrier such as a fatty oil. In addition, dosage unit forms can contain various other materials which modify the physical form of the dosage unit, for example, coatings of sugar, shellac, or other enteric agents.

The compounds can be administered as a component of an elixir, suspension, syrup, wafer, orally disintegrating film, orally disintegrating tablet, chewing gum or the like. A syrup may contain, in addition to the active compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors.

Solutions or suspensions used for injection can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates

and agents for the adjustment of tonicity such as sodium chloride, mannitol and dextrose. An injectable preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

Combined Oral Dosage Forms

As discussed above, the invention provides versatile combined oral dosage forms of palonosetron and an NK1 antagonist that can be readily modified depending on the therapeutic objective, and that do not present issues of stability and degradation. In a preferred embodiment, the invention provides a capsule for oral administration made from a hard outer shell that houses one or more NK1 antagonist tablets and one or more palonosetron soft-gel capsules. The finished capsule and the tablet(s) and soft-gel capsule(s) housed within the capsule shell are all preferably formulated as immediate release dosage forms. Netupitant and casopitant, and their pharmaceutically acceptable salts, are particularly preferred NK1 antagonists for the combined oral dosage forms of this invention.

While the NK1 antagonist is preferably formulated in a solid tablet, it will be understood that it can be formulated in any solid form that is suitable for oral administration including, for example, a tablet or capsule (hard or soft-gel). In a preferred embodiment, the NK1 antagonist is formulated in a tablet. The number of NK1 antagonist units contained within the combined dosage form can be, for example, from 1 to 10, 1 to 5, or 1 to 3. The netupitant units within the combined dosage form can provide anywhere from 50 to 500 mg of netupitant on an aggregate basis, preferably from 100 to 350 mg. Each netupitant unit preferably comprises from 50 to 200 mg of netupitant, more preferably 100 to 150 mg of netupitant, and most preferably 100 or 150 mg of netupitant.

The palonosetron can also be formulated in any solid form that is suitable for oral administration, although it is preferably formulated as a soft-gel capsule. Non-limiting examples of suitable palonosetron soft-gel capsules are provided in PCT publication WO 2008/049552, the contents of which are hereby incorporated by reference. The number of palonosetron units within the combined dosage from can be, for example, from 1 to 5, from 1 to 3 or just 1. Each of the palonosetron units within the combined dosage form can provide anywhere from 0.01 to 5.0 mg palonosetron, preferably from 0.1 to 1.0 mg palonosetron on an aggregate basis. Each

palonosetron unit will preferably comprise from 0.1 to 1.0 mg of palonosetron, most preferably about 0.25, 0.5, 0.75 or 1.0 mg of palonosetron.

Figure 1 illustrates an exemplary embodiment of a combined oral dosage form of palonosetron and netupitant. The dosage form 10 comprises a two piece hard outer shell that includes a body 20 and a cap 22. The dosage form 10 contains one palonosetron soft-gel capsule 30 (preferably containing 0.5 mg of palonosetron) and three netupitant tablets 40 (each preferably containing 100 mg of netupitant).

Hard Outer Shell

The hard outer shell of the present invention can be made of any pharmaceutically acceptable material that dissolves in gastric fluids. Preferred materials for the hard outer shell include, for example, gelatin, cellulose, starch, or hydroxypropyl methylcellulose (HPMC). In a particular embodiment of the invention, the hard outer shell has a maximum oxygen permeability. Preferably, the oxygen permeability is less about 1.0×10^{-3}, 5.0×10^{-4}, 1.0×10^{-4}, 5.0×10^{-5}, or even 2.0×10^{-5} ml·cm/(cm^2·24 hr. atm).

The hard outer shell can be a continuous structure. Alternatively, the hard outer shell can be a two-piece hard capsule.

Soft-Gel Capsule

The soft-gel capsule used for the palonosetron preferably comprises a soft outer shell and a liquid inner fill composition comprising palonosetron hydrochloride. Non-limiting examples of suitable palonosetron soft-gel capsules are provided in PCT publication WO 2008/049552, the contents of which are hereby incorporated by reference.

The soft outer shell of the soft-gel capsule can contain any type of material that dissolves in gastric fluids. Preferred materials for the soft outer shell include, for example, gelatin, cellulose, starch, or hydroxypropyl methylcellulose (HPMC). The soft-gel capsule can further comprise shell excipients such as glycerin, sorbitol, and colorants/opacifers such as titanium dioxide. The soft-gel capsule can further include solvents such as purified water. In particular embodiments of the invention, the outer shell has a maximum oxygen permeability, preferably of no more than 1.0×10^{-3}, 5.0×10^{-4}, 1.0×10^{-4}, 5.0×10^{-5}, or even 2.0×10^{-5} ml·cm/(cm^2·24 hr.

atm). Suitable soft-gel capsules include the 1.5-oval gelatine capsule shell manufactured by Catalent Pharma Solutions.

The liquid fill is preferably composed predominantly of one or more lipophilic components in an amount of from 50 wt.% to 99 wt.%, preferably from 75 wt.% to 98 wt.%. Preferred lipophilic components include, for example, mono- and di-glycerides of fatty acids, especially including the mono- and di-glycerides of capryl/capric acid. The liquid fill may also contain glycerin, preferably in an amount of from 1 to 15 wt.%, more preferably from 2 to 10 wt.%. In one preferred embodiment, both the shell and the inner fill composition comprise glycerin. In another preferred embodiment, the liquid fill comprises about 0.25, 0.50, 0.75 mg., or more of palonosetron as palonosetron hydrochloride.

The fill composition may comprise various means to facilitate the transition of palonosetron from the dosage form to the gastrointestinal fluids of the GI tract, so that the palonosetron may be more readily absorbed into the bloodstream. For example, the liquid fill composition may contain a surfactant, optimally in an amount of from 0.1 wt.% to 6 wt.%, from 0.5 wt.% to 5 wt.%, or from 1.0 wt.% to 3.0 wt.%. The liquid fill composition preferably comprises greater than 0.1, 0.5, or 1.0 wt.% of surfactant, and less than 10, 8, 5, 4, or even 4 wt.% of surfactant. A particularly preferred surfactant is polyglyceryl oleate.

Alternatively or in addition, the transitioning means for a liquid filled capsule may comprise water that forms a single phase or microemulsion with the other liquid ingredients in the excipient base. The liquid fill composition preferably comprises from 0.05 wt.% to 30 wt.% water, from 1 wt.% to 20 wt.% water, or from 2 wt.% to10 wt.% water. The liquid fill preferably comprises greater than 0.1, 0.5 or 1.0 wt.% water, and less than 20, 15, 10, 8 or 5 wt.% water.

The active agent, which is preferably palonosetron hydrochloride, is preferably present in the fill composition in an amount ranging from 0.01 to 10.0 wt.%, from 0.05 to 5.0 wt.%, or from 0.1 wt.% to 2.0 wt.%. Alternatively, particularly stable formulations have been found where the concentration of palonosetron exceeds 0.3%, preferably at a concentration no greater than 1 wt.%.

Tablet

The tablets of the present invention can include from 20 to 95 wt.% of NK1 antagonist (preferably netupitant), and preferably comprises from 60 to 80 wt.% of netupitant. In addition,

the tablets can contain diluents, disintegrants, surfactants, binders, glidants, and/or lubricants. In a particular embodiment, the tablet comprises from 5 to 25 wt.% of microcrystalline cellulose. The microcrystalline cellulose can function as a diluent and disintegrant, and preferably comprises 15 wt.% of the tablet. Another suitable disintegrant is sodium croscaramellose, which can be present in the tablet in an amount of from 1 to 5 wt.%, preferably 2 wt.%.

A suitable binder for use in the tablet is polyvinylpyrrolidone, which can be present in the tablet in an amount from 1 to 10 wt.% of the tablet, and preferably 5 wt.%. A suitable glidant for use in the tablet is colloidal silicon dioxide, which can be present in the tablet in an amount of 2 wt.%. Suitable lubricants for use in the tablet include sodium stearyl fumarate and magnesium stearate, which can be present in the tablet in an amount of 0.7 wt.% and 0.35 wt.%, respectively.

Application of The Combined Oral Dosage Forms

The invention further provides a method of treating emesis comprising orally administering to a patient suffering from emesis, or at risk for suffering emesis, a dosage form of the present invention. In still further embodiments, the invention provides methods of treating emesis by administering one or more of the dosage forms described herein. The dosage form is preferably administered shortly before the emesis inducing event (i.e. no more than 2 hours before the event). The emesis may be acute phase emesis (i.e. emesis experienced within about 24 hours of an emesis inducing event), or delayed emesis (i.e. emesis experienced after the acute phase, but within seven, six, five or four days of an emesis inducing event). The emesis may constitute chemotherapy induced nausea and vomiting ("CINV"), from moderately or highly emetogenic chemotherapy, radiation therapy induced nausea and vomiting ("RINV"), or post-operative nausea and vomiting ("PONV").

EXAMPLES

The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how the compounds claimed herein are made and evaluated, and are intended to be purely exemplary of the invention and are not intended to limit the scope of what the inventors regard as their invention. Efforts have been made to ensure accuracy with respect to numbers (e.g., amounts, temperature, etc.) but some errors and

deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, temperature is in °C or is at room temperature, and pressure is at or near atmospheric.

EXAMPLE 1 – PREPARATION OF ORAL DOSAGE FORM

In a preferred embodiment the combination is administered in a capsule oral dosage form, wherein the capsule houses one or more soft-gel capsules for the palonosetron and one or more hard tablets for the netupitant. Table 1 below describes a representative formulation for a soft-gel capsule containing 0.5 mg of palonosetron, suitable for inclusion in such a hard outer shell.

TABLE 1: REPRESENTATIVE SOFT-GEL FORMULATION

Ingredient	Approximate Amount (mg/Capsule)	Function
Fill Solution		
Palonosetron HCl	0.56[1]	Active
Mono- and di-glycerides of Capryl/Capric Acid (Capmul MCM)	62.19	Solvent vehicle
Glycerin, anhydrous, USP/Ph Eur	3.37	Plasticizer
Polyglyceryl oleate (Plurol Oleique CC 497)	0.87	Surfactant
Purified water, USP/Ph Eur	2.94	Co-solvent
Butylated hydroxyanisole (BHA), NF/Ph Eur	0.07	Antioxidant
Nitrogen	-	
Theoretical fill weight	70.00 mg	
Gelatine Capsule Shell, 1.5-oval (Catalent Pharma Solutions)[2]		
Gelatine (type 195), NF/Ph Eur	-	Shell
Sorbitol Special/Glycerin Blend 50/50	-	Plasticizer
Titanium dioxide, USP/Ph Eur	-	Colorant/Opacifier
Purified water, USP/Ph Eur	-	Solvent

[1]Corresponds to 0.50 mg. free base
[2]Quantitative composition of capsule shell is proprietary to Catalent Pharma Solutions

Table 2 below describes a representative formulation for a tablet containing 100 mg. of netupitant, suitable for inclusion in a hard shell.

TABLE 2: REPRESENTATIVE TABLET FORMULATION

Ingredient	Approximate Amount (mg/Tablet)	Function
Netupitant, milled	100	Active
Microcrystalline cellulose pH 101	20.5	Diluent and disintegrant
Sucrose Lauric Acid Esters	10.0	Surfactant
Polyvinilpyrrolidone K30	7.0	Binder
Sodium croscaramellose	3.0	Disintegrant
Colloidal Silicon Dioxide	3.0	Glidant
Sodium Stearyl Fumarate	1.0	Lubricant
Magnesium Stearate	0.5	Lubricant
Total weight	145 mg	

EXAMPLE 2 – PHARMACOKINETICS OF COMBINED DOSAGE FORM

Objective

The effects of palonosetron on the pharmacokinetics (PK) of netupitant and the effects of netupitant on the PK of palonosetron were examined in healthy volunteers.

Methods

A randomized, open, 3-way crossover study was conducted. Each subject participated in 3 treatment periods, each lasting approximately 12 days (Day -1 to Day 11). The treatment periods were separated by wash-out periods of no less than 14 days (between Day 1 of any 2 consecutive treatment periods).

The following treatments were investigated:

Treatment A: oral netupitant 450 mg. administered as single dose of three 150 mg. capsules.

Treatment B: oral palonosetron 0.75 mg. and oral netupitant 450 mg. administered simultaneously as three capsules of 150 mg. netupitant followed by 1 capsule of 0.75 mg. palonosetron.

Treatment C: oral palonosetron 0.75 mg. administered as single dose as one 0.75 mg. capsule.

Doses were administered under fasting conditions. Subjects fasted over-night for approximately 10 hours. Water, however, was permitted up to 1 hour pre-dose. Food intake was permitted 4 hours post-dose, and water was allowed ad libitum 1 hour post-dose.

Doses were administered with the subject in an upright position. The subjects remained in an upright position for 4 hours post-dose. The capsules were swallowed whole with 250 mL of room-temperature tap water. Repeated PK blood sampling (for netupitant and/or palonosetron) was performed.

Results

The primary PK variables assessed for netupitant and palonosetron were the maximum plasma concentration observed (C_{max}), the area under the plasma concentration versus time curve from time zero to the last quantifiable sampling time point (t) (AUC_{0-t}), and the area under the plasma concentration versus time curve from time zero to infinity (AUC_{0-inf}). The secondary PK variables assessed were the terminal elimination half-life ($t_{1/2,z}$), and the time at which the maximum plasma concentration was observed (t_{max}). Results are depicted in below Tables 3 and 4, as well as Figures 2 and 3.

Table 3: Summary of Netupitant Pharmacokinetic Parameters

Parameter	Netupitant 450 mg	Palonosetron 0.75 mg + Netupitant 450 mg
AUC_{0-t} [h*µg/L]	22808 (7270)	22775 (10064)
AUC_{0-inf} [h*µg/L]	25927 (10156)	26241 (13219)
C_{max} [µg/L]	650.2 (257.8)	659.7 (325.7)
t_{max} (h)	4.50 (3.00 ; 24.00)	4.50 (3.00 ; 23.95)
$t_{½,z}$ (h)	71.81 (37.10 ; 261.61)	78.31 (50.17 ; 196.13)

Mean and SD are shown, except for t_{max} and $t_{½}$, where median and range are shown.

As can be seen in Table 4 below, palonosetron shows a better pharmacokinetic profile when combined with Netupitant as opposed to administered as a single dose of palonosetron, for example, the greater AUC, the larger C_{max}, the shorter t_{max} (the median t_{max} was 0.5 hour shorter after administration of palonosetron in combination with netupitant), and the longer $t_{½,z}$.

Table 4: Summary of Palonosetron Pharmacokinetic Parameters

Parameter	Palonosetron 0.75 mg	Palonosetron 0.75 mg + Netupitant 450 mg
AUC_{0-t} [h*µg/L]	67415 (19554)	74230 (24866)
AUC_{0-inf} [h*µg/L]	70813 (20415)	77254 (25402)
C_{max} [µg/L]	1638.4 (415.5)	1863.1 (487.1)
t_{max} (h)	5.02 (4.00 ; 8.00)	4.50 (3.00 ; 6.02)
$t_{½,z}$ (h)	34.73 (19.61 ; 70.46)	36.91 (20.23 ; 56.08)

Mean and SD are shown, except for t_{max} and $t_{½}$, where median and range are shown.

EXAMPLE 3: NETUPITANT + DEXAMETHASONE DRUG INTERACTION STUDY

The effect of netupitant on orally administered dexamethasone pharmacokinetics was evaluated in this study. This was a randomized, open, 3-period crossover study utilizing an incomplete Latin Square design where subjects were given dexamethasone alone, or oral Netupitant 100 mg., 300 mg. or 450 mg. each given with dexamethasone. Netupitant was given orally on Day 1 only. The dexamethasone regimen for each treatment was 20 mg. orally Day 1, followed by 8 mg. orally every 12 hours from Day 2 through Day 4. Nineteen subjects (12 male and 7 female) completed the study (i.e., all 3 treatment periods).

Mean plasma concentrations of dexamethasone were higher when dexamethasone was co-administered with netupitant (Figure 4). The increase appeared to be dependant on the netupitant exposure.

The AUC_{0-24} (Day 1) of dexamethasone increased 1.5, 1.7 and 1.8-fold with co-administration of 100, 300 and 450 mg. netupitant, respectively. The AUC_{24-36} (Day 2) of dexamethasone increased 2.1, 2.4 and 2.6-fold and AUC_{84-108} and AUC_{84-inf} (Day 4) increased 1.7, 2.4 and 2.7-fold, with co-administration of 100, 300 and 450 mg. netupitant, respectively. Dexamethasone C_{max} on Day 1 was only slightly affected by co-administration of netupitant (1.1-fold increase during co-administration with 100 and 300 mg. netupitant, respectively, and 1.2-fold increase during co-administration with 450 mg. netupitant). C_{max} on Day 2 and Day 4 was increased approximately 1.7-fold in subjects administered netupitant. Dexamethasone C_{min} on Days 2-4 was increased approximately 2.8, 4.3 and 4.6-fold with co-administration of 100, 300 and 450 mg. netupitant, respectively. This clearly shows that the co-administration of netupitant and dexamethasone enhances the bioavailability of dexamethasone and provides a better therapeutic window of dexamethasone.

EXAMPLE 4: NETUPITANT PET RECEPTOR OCCUPANCY STUDY

This was a randomized, open-label, positron emission tomography (PET) study using 11C-GR205171 as tracer in 6 healthy male volunteers (2 per dose level) receiving single doses of netupitant (100, 300 or 450 mg) to investigate the degree of occupancy of NK_1 receptors in human brain, and to determine the relationship between plasma concentration of netupitant and NK_1 receptor occupancy (RO).

The anticipated high NK_1-RO (90% or higher) close to the expected C_{max} (6 hours post dose) was reached for striatum, occipital cortex, frontal cortex and anterior cingulate in 3 of 6 subjects of whom 1 received 300 mg. and 2 received 450 mg. of netupitant as a single oral dose.

All doses showed a relatively long duration of blockade of NK_1 receptors and the decline over time was dose dependent. In the 100 mg. dose group, 4 of 6 regions still had a mean NK_1-RO over 70% at 96 hours post dose. In the highest dose group (450 mg), 5 of 6 regions had a mean NK_1-RO of 80% or higher at 96 hours post dose. A comparison of the results for the dose groups (100 mg., 300 mg. and 450 mg) showed a consistent but small increase in NK_1-ROs with increasing netupitant dose. (Figure 5)

EXAMPLE 5: CLINICAL EFFICACY STUDY

A phase 2 trial evaluated three single doses of netupitant combined with palonosetron and dexamethasone compared to palonosetron alone and dexamethasone to obtain dose ranging information for netupitant used with oral palonosetron in the CINV patient population.

The objective of the study was to compare the efficacy and safety of three single oral doses of netupitant combined with oral palonosetron and given with dexamethasone, versus oral palonosetron-alone given with dexamethasone (without netupitant) for the prevention of highly emetogenic chemotherapy (HEC)-induced nausea and vomiting. The FDA-approved oral aprepitant regimen given with IV ondansetron and dexamethasone was included in the study as an active comparator for exploratory purposes. The FDA-approved oral palonosetron 0.5 mg. dose was used in each applicable treatment group in this study.

This was a multicenter, randomized, double-blind, double-dummy, parallel group, stratified study. Eligible patients were randomized (stratified by gender) to one of the following treatment groups:

Group 1 – 0.5 mg. oral palonosetron on Day 1 (with an oral dexamethasone standard regimen: 20 mg. on Day 1 and 8 mg. BID from Day 2 through Day 4)

Group 2 – 100 mg. oral netupitant plus 0.5 mg. oral palonosetron on Day 1 (with an oral dexamethasone adjusted regimen*: 12 mg. on Day 1 and 8 mg. daily from Day 2 through Day 4)

Group 3 – 200 mg. oral netupitant plus 0.5 mg. oral palonosetron on Day 1 (with an oral dexamethasone adjusted regimen*: 12 mg. on Day 1 and 8 mg. daily from Day 2 to Day 4)

Group 4 – 300 mg. oral netupitant plus 0.5 mg. oral palonosetron on Day 1 (with dexamethasone adjusted regimen*: 12 mg. on Day 1 and 8 mg. daily from Day 2 to Day 4)

Group 5 – 125 mg. oral aprepitant plus IV ondansetron 32 mg. (both on Day 1) then 80 mg. oral aprepitant on Day 2 and Day 3, (all with an oral dexamethasone adjusted regimen: 12 mg. on Day 1 and 8 mg. daily from Day 2 through Day 4)

In addition, a Group 6 was added to the analysis for comparative purposes, based on the results reported by Grunberg et al., Support Cancer Care (2009) 17:589-594:

Group 6 – 285 mg. oral aprepitant plus 20 mg. oral dexamethasone plus 0.2 mg. palonosetron i.v. (all on Day 1) then 80 mg. oral aprepitant

The primary efficacy endpoint was the complete response rate (defined as no emetic episodes, no rescue medication) within 120 hours after the start of the highly emetogenic chemotherapy administration. Secondary efficacy endpoints were:

- Complete response for the 0-24 hour interval (acute phase); and for the 25-120 hour interval (delayed phase);
- Complete protection (defined as no emesis, no rescue therapy, no significant nausea); Total control (defined as no emesis, no rescue therapy and no nausea); No nausea (maximum VAS <5 mm); No significant nausea (maximumVAS <25 mm); No rescue medication; No emesis. These endpoints were evaluated for the 0-120 hour interval (overall), acute and delayed phase.
- Time to first emetic episode, Time to first rescue medication, Time to treatment failure (based on time to the first emetic episode or time to the first rescue medication, whichever occurs first);

- Severity of nausea for the overall, acute and delayed phase; • Patient global satisfaction with anti-emetic therapy by means of VAS for each 24 hour interval.

Complete response rates are summarized in Table 5. The percent of patients with complete response over 0-120 hours after start of cisplatin administration was 76.5% in the palonosetron alone group and 87.4%, 87.6%, and 89.6% in the netupitant 100 mg., 200 mg., and 300 mg. groups, respectively. Differences from palonosetron-alone were greater than 10% (10.9% to 13.2%). All doses of netupitant were statistically superior to palonosetron alone (p-value=0.004 for the netupitant 300 mg. combination group).

TABLE 5: COMPLETE RESPONSE RATE FOR THE OVERALL, ACUTE AND DELAYED PHASE: MFAS Population

Efficacy endpoint	Palo alone (n=136)	Palo + Netu 100 mg (n=135)	Palo + Netu 200 mg (n=137)	Palo + Netu 300 mg (n=135)	Aprepitant Regimen (N=134)
CR, Overall Phase, 0-120h					
Percent of Patients	76.5	87.4	87.6	89.6	86.6
Difference from Palo alone (%)		10.9	11.1	13.2	10.1
p-value (*)		0.018	0.017	0.004	0.027
CR, Acute Phase, 0-24h					
Percent of Patients	89.7	93.3	92.7	98.5	94.8
Difference from Palo alone (%)		3.6	3.0	8.8	5.1
p-value (*)		0.278	0.383	0.007	0.114
CR, Delayed Phase, 25-120h					
Percent of Patients	80.1	90.4	91.2	90.4	88.8
Difference from Palo alone (%)		10.2	11.1	10.2	8.7
p-value (*)		0.018	0.010	0.018	0.043

(*) p-value from logistic regression analysis, aprepitant p-value from post-hoc logistic regression analysis.

Table 6 summarizes results for main secondary endpoints. In the overall phase, 76.5% of patients in the palonosetron-alone group did not experience emesis, while 87.4, 87.6, and 91.1% of patients did not experience emesis in the netupitant 100 mg., 200 mg. and 300 mg. combination groups, respectively ($p<0.05$ for all doses).

TABLE 6: SUMMARY OF SECONDARY EFFICACY
RESULTS: PERCENT OF PATIENTS, MFAS POPULATION

Efficacy endpoint	Palo alone (n=136)	Palo + Netu 100 mg (n=135)	Palo + Netu 200 mg (n=137)	Palo + Netu 300 mg (n=135)	Aprepitant Regimen (N=134)	Palo+Aprep 285 mg (N=41) **
No Emesis						
Overall	76.5	87.4*	87.6*	91.1*	87.3*	
Acute	89.7	93.3	92.7	98.5*	94.8	
Delayed	80.1	90.4*	91.2*	91.9*	89.6*	
No Rescue						
Overall	95.6	97.8	100	98.5	97.8	
Acute	97.8	99.3	100	100	100	
Delayed	97.1	97.8	100	98.5	97.8	
No Nausea						
Overall	50.7	54.8	62.0	61.5	58.2	32
Acute	75.0	72.6	77.4	80.0	77.6	59
Delayed	53.7	59.3	65.0	68.1*	60.4	41
No Significant Nausea						
Overall	79.4	80.0	86.1	89.6*	85.8	56
Acute	93.4	94.1	94.2	98.5*	94.0	79
Delayed	80.9	81.5	89.8*	90.4*	88.1	59
Total Control						
Overall	50.0	54.8	61.3	59.3	56.0	
Acute	71.3	71.9	76.6	80.0	74.6	
Delayed	52.2	59.3	65.0*	65.9*	58.2	
Complete Protection						
Overall	69.9	76.3	80.3*	83.0*	78.4	51
Acute	87.5	89.6	88.3	97.0*	89.6	76
Delayed	73.5	80.0	87.6*	84.4*	82.1	66

* p-value <0.05 compared with palonosetron-alone; aprepitant comparisons p-values calculated by post-hoc analysis
** As reported by Grunberg *et al.*, Support Cancer Care (2009) 17:589-594

EXAMPLE 7: COMPARATIVE RESULTS OF APREPITANT DOSING REGIMEN

The following Table 8 reports the results observed for an aprepitant dosing regimen, as described in the FDA approved prescribing information for aprepitant, which demonstrates, among other things, that aprepitant has no meaningful effect on nausea. Table 7 reports the dosing regimen:

TABLE 7

Treatment Regimen	Day 1	Days 2 to 4
Aprepitant	Aprepitant 125 mg PO Dexamethasone 12 mg PO Ondansetron 32 mg I.V.	Aprepitant 80 mg PO Daily (Days 2 and 3 only) Dexamethasone 8 mg PO Daily (morning)

TABLE 8

Percent of Patients Receiving Highly Emetogenic Chemotherapy Responding by Treatment Group and Phase for Study 1 — Cycle 1

ENDPOINTS	Aprepitant Regimen (N = 260)[†] %	Standard Therapy (N = 261)[†] %	p-Value
PRIMARY ENDPOINT			
Complete Response			
Overall[‡]	73	52	<0.001
OTHER PRESPECIFIED ENDPOINTS			
Complete Response			
Acute phase[§]	89	78	<0.001
Delayed phase[‖]	75	56	<0.001
Complete Protection			
Overall	63	48	0.001
Acute phase	85	75	NS*
Delayed phase	66	52	<0.001
No Emesis			
Overall	78	55	<0.001
Acute phase	90	79	0.001
Delayed phase	81	59	<0.001
No Nausea			
Overall	48	44	NS*
Delayed phase	51	48	NS*
No Significant Nausea			
Overall	73	66	NS*
Delayed phase	75	69	NS*

[†]N: Number of patients (older than 18 years of age) who received cisplatin, study drug, and had at least one post-treatment efficacy evaluation.
[‡]Overall: 0 to 120 hours post-cisplatin treatment.
[§]Acute phase: 0 to 24 hours post-cisplatin treatment.
[‖]Delayed phase: 25 to 120 hours post-cisplatin treatment.
*Not statistically significant when adjusted for multiple comparisons.

****

Throughout this application, various publications are referenced. The disclosures of these publications in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art to which this invention pertains. It will be apparent to those skilled in the art that various modifications and variations can be made in the present invention without departing from the scope or spirit of the invention. Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims.

CLAIMS

1) A method of treating nausea and vomiting for five consecutive days in a patient in need thereof, comprising:

a) administering to said patient on day one netupinant or a pharmaceutically acceptable salt thereof, in a therapeutically effective amount which is effective to treat nausea and vomiting during the acute and delayed phases of emesis, and which enters the systemic circulation, crosses the blood brain barrier and occupies at least 70% of NK_1 receptors in the striatum seventy-two hours after said administration;

b) administering to said patient on day one a therapeutically effective amount of a 5-HT_3 antagonist or a pharmaceutically acceptable salt thereof, which is effective to treat nausea and vomiting during the acute and delayed phases; and

c) administering to said patient on day one a first dose of dexamethasone which is ineffective against nausea and vomiting when administered alone, but effective against nausea and vomiting when administered in combination with said netupitant, wherein said first dose comprises from 50 to 70% of a minimum effective dose when administered alone.

2) The method of claim 1, further comprising: d) administering to said patient, on days two, three and four, a second dose of dexamethasone which is ineffective against nausea and vomiting when administered alone, but effective against nausea and vomiting when administered in combination with said netupitant, wherein said second dose comprises from 40 to 60% of a minimum effective dose when administered alone.

3) The method of claim 1 or 2, wherein said netupitant occupies at least 80% of NK_1 receptors in the striatum seventy-two hours after said administration.

4) The method of any one of claims 1 to 3, wherein only one dose of netupitant or a pharmaceutically acceptable salt thereof is administered during said five days.

5) The method of any one of claims 1 to 4, wherein only one dose of netupitant or a pharmaceutically acceptable salt thereof is administered during said five days, and said one dose is administered orally.

6) The method of any one of claims 1 to 5, wherein said therapeutically effective amount of netupitant comprises from about 200 to about 400 mg. of netupitant or a pharmaceutically acceptable salt thereof.

7) The method of any one of claims 1 to 6, wherein said therapeutically effective amount of netupitant comprises about 300 mg. of netupitant as a free base.

8) The method of any one of claims 1 to 7, wherein said therapeutically minimum effective dose of dexamethasone when administered alone comprises from about 16 mg to about 20 mg of dexamethasone.

9) The method of any one of claims 1 to 8, wherein only one dose of 5-HT_3 antagonist or a pharmaceutically acceptable salt thereof is administered during said five days.

10) The method of any one of claims 1 to 9, wherein the 5-HT_3 antagonist is ondansetron or palonosetron.

11) The method of any one of claims 1 to 10, wherein said therapeutically effective amount of 5-HT_3 antagonist comprises from about 0.25 to about 0.75 mg. of palonosetron or a pharmaceutically acceptable salt thereof.

12) The method of any one of claims 1 to 11, wherein said therapeutically effective amount of 5-HT_3 antagonist comprises about 0.56 mg. of palonosetron hydrochloride, corresponding to about 0.5 mg of palonosetron as a free base.

13) The method of any one of claims 1 to 12, wherein said palonosetron is administered orally.

14) The method of any one of claims 1 to 13, comprising orally administering:

a) about 300 mg. of netupitant as a free base on day one;

b) about 0.56 mg. of palonosetron hydrochloride, corresponding to about 0.5 mg of palonosetron as a free base, on day one; and

c) about 12 mg. of dexamethasone on day one.

15) The method of any one of claims 1 to 14, comprising orally administering:

a) about 300 mg. of netupitant as a free base on day one;

b) about 0.56 mg. of palonosetron hydrochloride (corresponding to about 0.5 mg of palonosetron as a free base) on day one;

c) about 12 mg. of dexamethasone on day one; and

d) about 8 mg. of dexamethasone on days two, three and four.

16) A method of treating nausea and vomiting for a period of five consecutive days in a patient in need thereof, comprising administering to said patient netupinant or a pharmaceutically acceptable salt thereof, in a therapeutically effective amount which is

effective to treat nausea and vomiting during the acute and delayed phases of emesis, and which enters the systemic circulation, crosses the blood brain barrier and occupies at least 70% of NK_1 receptors in the striatum seventy-two hours after said administration.

17) The method of claim 16, wherein said netupitant occupies at least 80% of NK_1 receptors in the striatum seventy-two hours after said administration

18) The method of claim 16 or 17, further comprising:

a) administering to said patient on day one a first dose of dexamethasone which is ineffective against nausea and vomiting when administered alone, but effective against nausea and vomiting when administered in combination with said netupitant, wherein said first dose comprises from 50 to 70% of a minimum effective dose when administered alone; and

b) if said patient is subject to highly emetogenic chemotherapy, administering to said patient, on days two, three and four, a second dose of dexamethasone which is ineffective against nausea and vomiting when administered alone, but effective against nausea and vomiting when administered in combination with said netupitant, wherein said second dose comprises from 40 to 60% of a minimum effective dose when administered alone.

19) The method of any one of claims 16 to 18, further comprising administering a therapeutically effective amount of a 5-HT_3 antagonist.

20) The method of any one of claims 16-19, wherein said therapeutically effective amount of netupitant comprises from about 200 to about 400 mg. of netupitant or a pharmaceutically acceptable salt thereof, said therapeutically effective amount of 5-HT_3 antagonist comprises from about 0.25 to about 0.75 mg. of palonosetron or a pharmaceutically acceptable salt thereof, and said therapeutically minimum effective dose of dexamethasone when administered alone comprises from about 16 mg to about 20 mg of dexamethasone.

21) The method of any one of claims 16-20, wherein:

a) only one dose of netupitant is administered during said five days on day one, comprising about 300 mg. of netupitant as the free base; and

b) administering about 12 mg. of dexamethasone on day one; and

c) if said patient is undergoing highly emetogenic chemotherapy, administering about 8 mg. of dexamethasone on days two, three and four.

22) The method of claim 21, further comprising administering only one dose of a 5-HT_3 antagonist during said five days on day one, comprising about 0.56 mg. of palonosetron hydrochloride, corresponding to about 0.5 mg of palonosetron as a free base.

23) The method of any one of claims 1-22, wherein said nausea and vomiting is chemotherapy induced nausea and vomiting ("CINV"), radiation therapy induced nausea and vomiting ("RINV"), or post-operative nausea and vomiting ("PONV").

24) The method of any one of claims 1-22, wherein said nausea and vomiting is induced by moderately or highly emetogenic chemotherapy.

25) The method of any one of claims 1-24, comprising administering moderately or highly emetogenic chemotherapy within from about one hour to about two hours of said administration of said netupitant or pharmaceutically acceptable salt thereof.

26) The method of any one of claims 1-25, comprising treating nausea and vomiting in response to highly emetogenic chemotherapy during the acute phase, or in response to highly emetogenic chemotherapy during the delayed phase, or in response to moderately emetogenic chemotherapy during the acute phase, or in response to moderately emetogenic chemotherapy during the delayed phase.

27) A method of treating nausea and vomiting in a human subject in need thereof, during the acute and/or delayed phases of CINV in response to moderately or highly emetogenic chemotherapy, comprising administering a therapeutically effective amount of netupitant, or a pharmaceutically acceptable salt thereof, and a therapeutically effective amount of palonosetron, or a pharmaceutically acceptable salt thereof, before said chemotherapy.

28) The method of claim 27, comprising orally administering from about 200 to about 400 mg. of netupitant or a pharmaceutically acceptable salt thereof, and from about 0.25 to about 0.75 mg. of palonosetron or a pharmaceutically acceptable salt thereof.

29) The method of claim 27 or 28, comprising orally administering about 300 mg. of netupitant as the free base, and about 0.56 mg. of palonosetron hydrochloride.

30) The method of any one of claims 27-29, further comprising, if said patient is subject to highly emetogenic chemotherapy, administering a sub-therapeutic dose of dexamethasone on days one, two, three and four.

31) The method of any one of claims 27-30, further comprising, if said patient is undergoing highly emetogenic chemotherapy, orally administering 12 mg. of dexamethasone on day one, and 8 mg. of dexamethasone on days two, three and four.

32) The method of any one of claims 1-31, wherein netupitant potentiates the therapeutic effect of dexamethasone.

33) The method of any one of claims 1-32, wherein netupitant promotes bioavailability of palonosetron.

34) An orally administered dosage form comprising a combination of palonosetron and an NK1 antagonist, or a pharmaceutically acceptable salt or prodrug thereof, comprising:

a) an outer shell;

b) one or more NK1 antagonist units housed within said outer shell, each comprising said netupitant or pharmaceutically acceptable salt or prodrug thereof and one or more pharmaceutically acceptable excipients; and

c) one or more palonosetron units housed within said outer shell, each comprising said palonosetron or pharmaceutically acceptable ester or prodrug thereof and one or more pharmaceutically acceptable excipients;

wherein said dosage form comprises (3S)-3-[(3aS)-1-oxo- 2,3,3a,4,5,6-hexahydro-1*H*-benzo[*de*] isoquinoline-2-yl]-1-azoniabicyclo[2.2.2]octan-1-olate in an amount that does not exceed 3 wt.%.

35) The dosage form of claim 34, comprising about 0.56 mg. of palonosetron hydrochloride and from about 100 to about 500 mg, or from about 200 to about 400 mg, or about 300 mg of netupitant or a pharmaceutically acceptable salt thereof.

36) The dosage form of claim 34 or 35, wherein said one or more NK1 antagonist units are in the form of one or more orally administered tablets, and said palonosetron units are in the form of one or more orally administered soft-gel capsules.

37) The dosage form of any one of claims 34 to 36, wherein each of said tablets comprises from about 50 to about 200 mg, or from about 100 to about 150 mg, or about 100 mg of netupitant.

38) The capsule of any one of claims 34 to 37, wherein said outer shell of said capsule has an oxygen permeability of less than 1.0×10^{-3} ml·cm/(cm^2·24 hr. atm).

39) The capsule of any one of claims 34 to 38, wherein each of said soft-gel capsules comprises an inner fill composition comprising from 0.1 to 2.0 mg. of palonosetron hydrochloride.

40) The capsule of any one of claims 34 to 39, wherein each of said soft-gel capsules comprises an inner fill composition comprising from 75 to 98 wt.% of one or more lipophilic components.

41) The capsule of any one of claims 34 to 40, wherein each of said soft-gel capsules comprises an outer shell having an oxygen permeability of less than 1.0×10^{-3} ml·cm/(cm^2·24 hr. atm).

42) An orally administered capsule dosage form comprising:

a) an outer shell;

b) one or more tablets housed within said outer shell, each comprising an NK1 antagonist or a pharmaceutically acceptable salt or prodrug thereof and one or more pharmaceutically acceptable excipients; and

c) one or more soft-gel capsules housed within said outer shell, each comprising palonosetron or a pharmaceutically acceptable ester or prodrug thereof and one or more pharmaceutically acceptable excipients;

wherein said dosage form comprises (3S)-3-[(3aS)-1-oxo-2,3,3a,4,5,6-hexahydro-1*H*-benzo[*de*] isoquinoline-2-yl]-1-azoniabicyclo[2.2.2]octan-1-olate in an amount that does not exceed 3 wt.%.

43) The capsule of claim 42 comprising about 0.56 mg. of palonosetron hydrochloride and from about 100 to about 500 mg, or from about 200 to about 400 mg, or about 300 mg of netupitant.

44) The capsule of claim 42 or 43, wherein said outer shell of said capsule has an oxygen permeability of less than 1.0×10^{-3} ml·cm/(cm^2·24 hr. atm).

45) The capsule of any one of claims 42 to 44, wherein each of said tablets comprises from about 50 to about 200 mg, or from about 100 to about 150 mg, or about 100 mg of netupitant or a pharmaceutically acceptable salt thereof.

46) The capsule of any one of claims 42 to 45, wherein each of said soft-gel capsules comprises an outer shell having an oxygen permeability of less than 1.0×10^{-3} ml·cm/(cm^2·24 hr. atm).

47) The capsule of any one of claims 42 to 46, wherein said soft-gel capsule comprises an inner fill composition comprising from 0.1 to 2.0 mg. of palonosetron hydrochloride.

48) The capsule of any one of claims 42 to 47, wherein said soft-gel capsule comprises an inner fill composition comprising from 75 to 98 wt.% of one or more lipophilic components.

49) The dosage form or capsule of any one of claims 34 to 48, wherein netupitant and palonosetron are formulated in separate form and then combined in one dosage.

50) A method of treating emesis comprising administering to a human in need thereof the dosage form of any one of claims 34-51.

51) The method of claim 50 wherein said emesis is delayed-onset emesis.

COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING

ABSTRACT

Provided are compositions and methods for treating or preventing nausea and vomiting in patients undergoing chemotherapy, radiotherapy, or surgery.

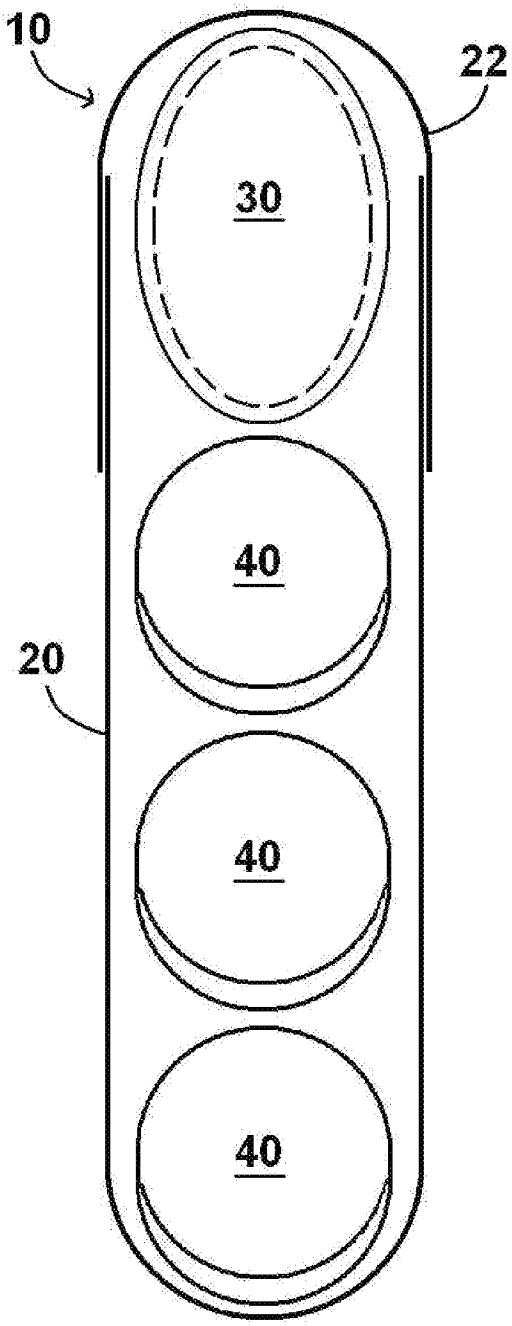


Figure 1

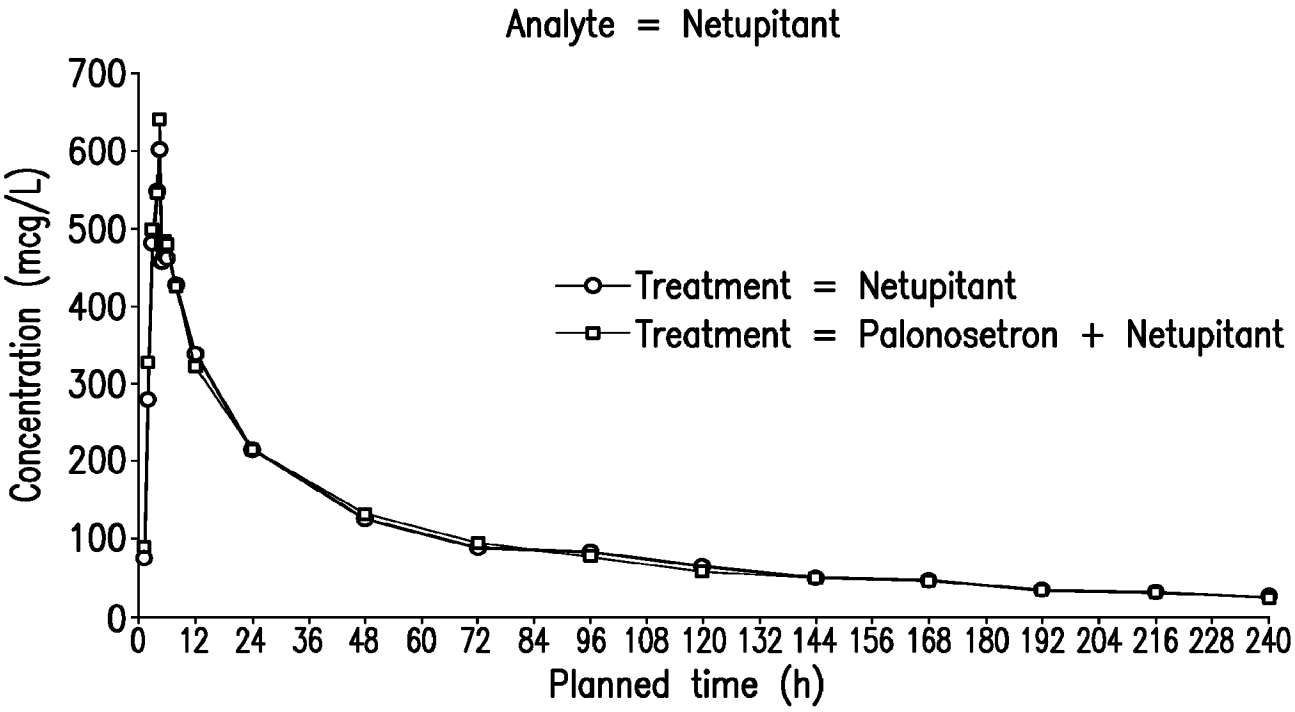

Analyte = Netupitant
Concentration (mcg/L)
700
600
500
400
300
200
100
0
0 12 24 36 48 60 72 84 96 108 120 132 144 156 168 180 192 204 216 228 240
Planned time (h)
Treatment = Netupitant
Treatment = Palonosetron + Netupitant

FIG.2

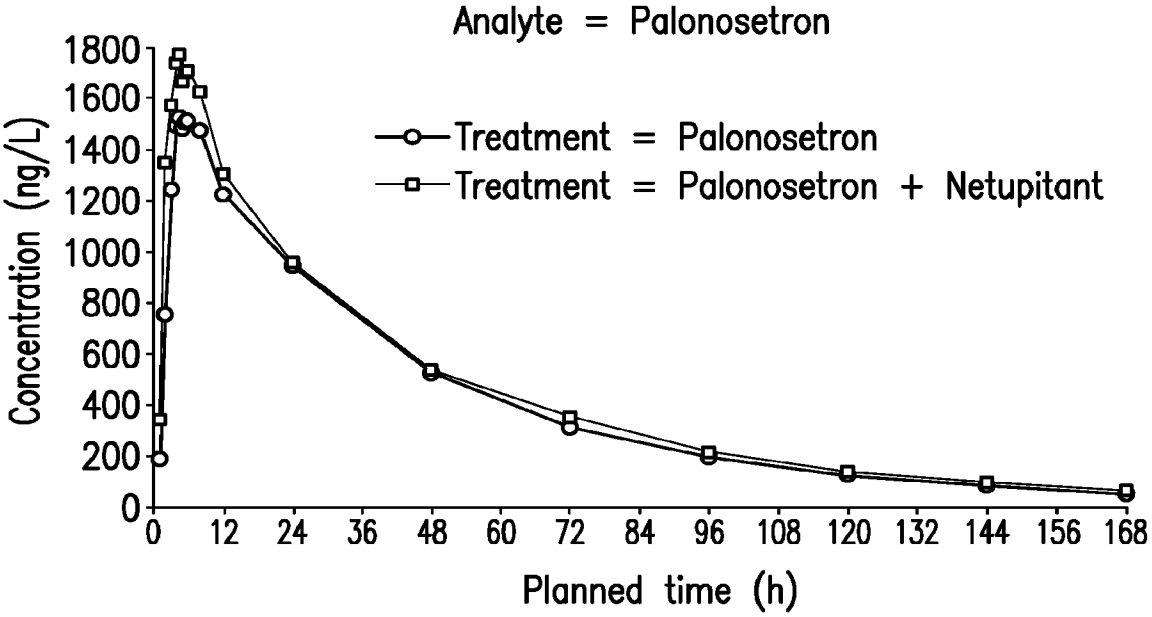

Analyte = Palonosetron
Treatment = Palonosetron
Treatment = Palonosetron + Netupitant
Concentration (ng/L)
1800
1600
1400
1200
1000
800
600
400
200
0
0
12
24
36
48
60
72
84
96
108
120
132
144
156
168
Planned time (h)

FIG.3

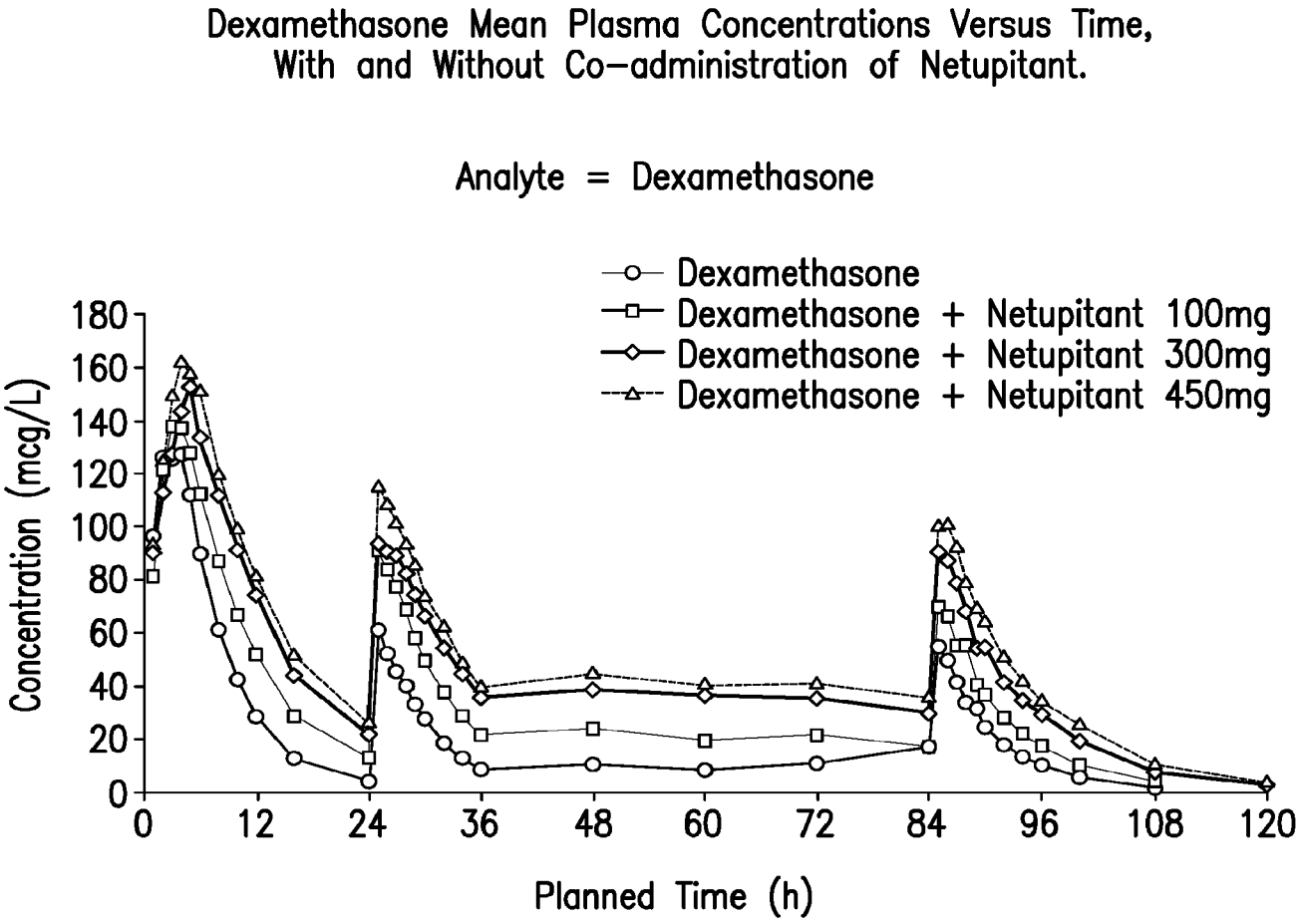

Dexamethasone Mean Plasma Concentrations Versus Time,
With and Without Co-administration of Netupitant.
Analyte = Dexamethasone
Dexamethasone
Dexamethasone + Netupitant 100mg
Dexamethasone + Netupitant 300mg
Dexamethasone + Netupitant 450mg
Concentration (mcg/L)
180
160
140
120
100
80
60
40
20
0
0
12
24
36
48
60
72
84
96
108
120
Planned Time (h)

FIG.4

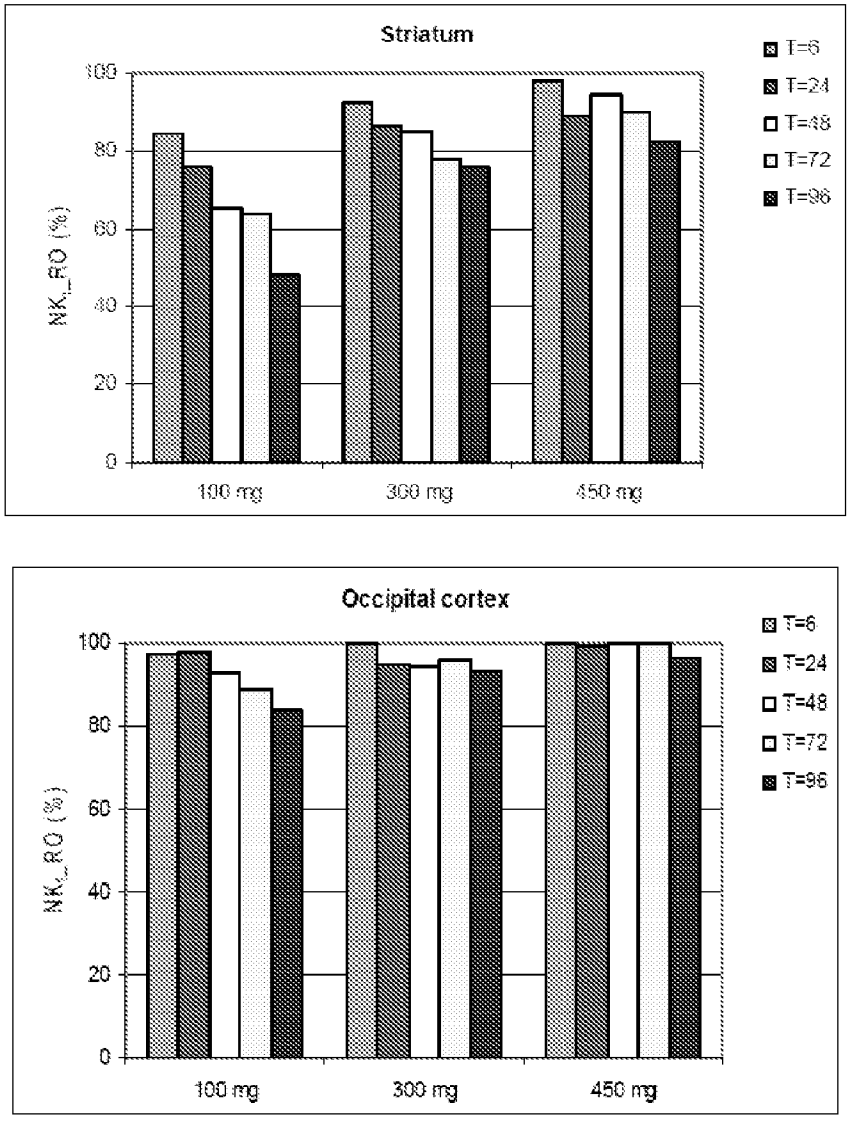

Striatum
NK_RO (%)
100
80
60
40
20
0
100 mg
300 mg
450 mg
T=6
T=24
T=48
T=72
T=96
Occipital cortex
NK_RO (%)
100
80
60
40
20
0
100 mg
300 mg
450 mg
T=6
T=24
T=48
T=72
T=96

FIG. 5

NONPROVISIONAL APPLICATION FOR UNITED STATES PATENT

for

COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING

by:

Fabio Trento, a citizen of Italy residing at Via Alla Valle 20B I-22020 Pare (Como - Italy); Sergio Cantoreggi, a citizen of Switzerland residing at Via ai Ronchi, 37 CH-6943 Vezia Switzerland; Giorgia Rossi, a citizen of Italy residing at Via della Liberta, 1A - 1-22012 Cernobbio (Como - Italy); Roberta Cannella, a citizen of Italy, residing at Via Al Colle, 42 - 1-21100 Varese, Italy; Daniele Bonadeo, a citizen of Italy residing at Via Ronco Capo Caccia, 32 - I- 21030 Casalzuigno, Varese, Italy

COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. Application No. 14/069,970, filed November 1, 2013, which is a continuation of U.S. Application No. 13/077, 462, filed March 31, 2011, now U.S. Patent No. 8,623,826, issued January 7, 2014, which is a continuation of International Application No. PCT/IB2010/003106, filed November 18, 2010, which claims priority to U.S. Provisional Application No. 61/262,470, filed November 18, 2009, and U.S. Provisional Application No. 61/382,709, filed September 14, 2010. All of the above applications are hereby incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

The present invention relates to the use of centrally acting NK_1 antagonists to treat nausea and vomiting, particular nausea and vomiting induced by highly emetogenic chemotherapy, and to the treatment of such nausea and vomiting over multiple consecutive days. The present invention also relates to combined oral dosage forms of palonosetron and netupitant.

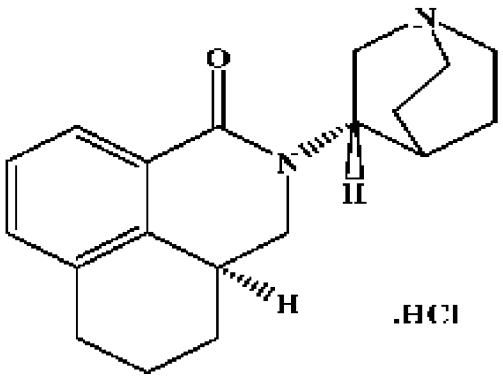
BACKGROUND OF THE INVENTION

With the development of the 5-HT_3 antagonist in the early 1990s, there emerged new strategies in the medical community to better control nausea and vomiting caused by various medical procedures, including chemotherapy (CINV), surgery (PONV), and radiation therapy (RINV). When added to steroids such as dexamethasone, several 5-HT_3 antagonists have been demonstrated to significantly improve the standard of life for patients undergoing emetogenic medical procedures. Examples of 5-HT_3 antagonists include ondansetron, marketed by GlaxoSmithKline, and palonosetron, developed by Helsinn Healthcare.

Palonosetron hydrochloride has recently emerged as a highly efficacious anti-nauseant and anti-emetic agent. See PCT publications WO 2004/045615 and 2004/073714 from Helsinn Healthcare. Palonosetron hydrochloride is sold in the United States as a sterile injectable liquid under the ALOXI® brand, in sterile unit dose vials containing 0.075 or 0.25 mg. of palonosetron

hydrochloride. Palonosetron hydrochloride also is also sold as an orally administered soft-gel dosage form containing 0.5 mg. of palonosetron hydrochloride.

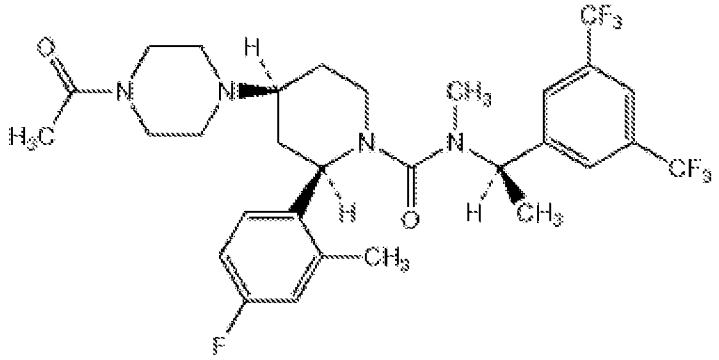
The official chemical name for palonosetron hydrochloride is (3aS)-2-[(S)-1-Azabicyclo [2.2.2] oct-3-y1]- 2,3,3a,4,5 ,6-hexahydro-l-oxo-l*H*beriz [*de*] isoquinoline hydrochloride (CAS No. 119904-90-4); its empirical formula is $C_{19}H_{24}N_2O{\cdot}HCl$, and its molecular weight is 332.87. The compound is represented by the following chemical structure:



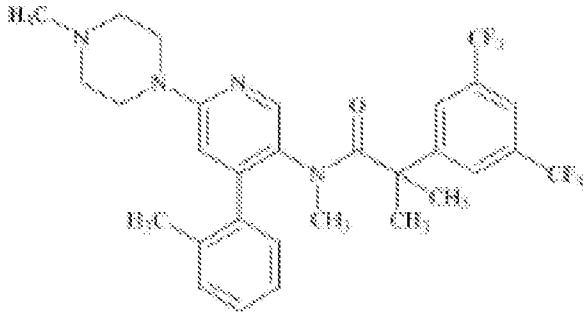
Methods of synthesizing palonosetron are described in U.S. Patent Nos. 5,202,333 and 5,510,486. Pharmaceutically acceptably dosage forms are described in PCT publications WO 2004/067005 and WO 2008/049552 from Helsinn Healthcare.

NK_1 antagonists have also recently emerged as a tool for combating nausea and vomiting from emetogenic medical procedures. Most recently, aprepitant was approved by the Food and Drug Administration ("FDA") for use in combination with other anti-emetic agents for the prevention of nausea and vomiting from moderately and highly emetogenic chemotherapy. However, it quickly became apparent that aprepitant's effect was limited principally to vomiting — not nausea — and that aprepitant did not provide as much benefit during the acute phase of CINV. When tested against nausea in humans, aprepitant was unable to induce a significant reduction in the incidence or severity of nausea following moderately or highly emetogenic chemotherapy when compared to a 5-HT_3 antagonist alone. See FDA Approved Labeling for Emend®. Thus, while aprepitant is approved by FDA for the prevention of nausea and vomiting in humans, this indication is somewhat misleading because aprepitant did not reduce nausea in the clinical trials preformed for aprepitant more than nausea controlled by the other components of the anti-emetic regimen. In addition, the results reported in Grunberg *et al.,* SUPPORT CANCER CARE (2009) 17:589-594, from a combined treatment of aprepitant and palonosetron, were far from promising.

Merck & Co. markets aprepitant, as EMEND® in the United States. The product is approved in a capsule dosage form, and is marketed for the prevention of CINV (acute and delayed) in combination with other anti-emetic agents such as ondansetron and metoclopramide. The product reportedly has a terminal half-life of from 9 to 13 hours. While aprepitant has demonstrated some effect against nausea, its effects have been inconsistent. Casopitant is another NK_1 antagonist that has been tested against nausea and vomiting in humans. A clinical study of casopitant is discussed in *Therapeutics and Clinical Risk Management* 2009:5 pp375-384 to Ruhlmann et al. and *Drug Metabolism and Disposition,* vol.37, No. 8, 2009, pp.1635-1645 to Pellegatti et al. As reported by Ruhlmann *et al.* in THERAPEUTICS AND CLINICAL RISK MANAGEMENT, 2009:5 375-384, casopitant had no statistically significant effect against nausea when administered in response to moderately emetogenic chemotherapy, and even induced nausea as a side effect. Casopitant has the formula (2*R*,4*S*)-4-(4-acetytlpiperazin-l-y1)-*N*-{(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethy1}-2-(4-fluoro-2-methylpheny1)-*N*-methylpiperidine-l-carboxamide, and the below chemical structure:



Netupitant is another selective NK_1 receptor antagonist under development by Helsinn Healthcare, having the formula 2-[3,5-bis(trifluoromethyl)phenyl]-N,2-dimethyl-N-[4-(2-methylpheny1)-6-(4-methylpiperazin-l-y1)pyridin-3-yl]propanamide, or Benzeneacetamide, N,α,α-trimethyl-N-[4-(2-methylpheny1)-6-(4-methyl-l-piperaziny1)-3-pyridinyl]-3,5-bis(trifluoromethyl)-, and the below chemical structure:



Methods of synthesizing and formulating netupitant and its prodrugs are described in U.S. Patent Nos. 6,297,375, 6,719,996 and 6,593,472 to Hoffmann La Roche.

Other representative NK_1 antagonists include ZD4974 (developed by AstraZeneca), CGP49823 (developed by Ciba-Geigy), Lanepitant and LY686017 (developed by Eli Lilly), FK888 (developed by Fujisawa), Vofopitant, Vestipitant and Orvepitant (developed by GlaxoSmithKline), Befetupitant (developed by Hoffmann-La Roche), R116031 (developed by Janssen), L-733060 and L-736281 (developed by Merck), TKA731, NKP608 and DNK333 (developed by Novartis), CP-96345, CP-99994, CP-122721, CJ-17493, CJ-11974 and CJ-11972 (developed by Pfizer), RP67580 and Dapitant (developed by Rhone-Poulenc Rorer), Nolpitantium and SSR240600 (developed by Sanofi-Aventis), SCH388714 and Rolapitant (developed by Schering-Plough), TAK637 (developed by Takeda), HSP117 (developed by Hisamitsu), KRP103 (developed by Kyorin Pharm) and SLV317 (developed by Solvay). Chemical structures of the above-mentioned NK_1 antagonists are shown below and discussion of those compounds as well as other NK_1 antagonists is present in *Expert Opin. Ther. Patents* (2010) 20(8), pp1019-1045 by Huang et al.

The background of U.S. Patent No. 6,297,375 suggests that NK_1 antagonists are useful for treating a variety of conditions in which substance P (the natural ligand for the NK_1 receptor) is active. These conditions include depression, pain (especially pain resulting from inflammatory conditions such as migraine, rheumatoid arthritis, asthma, and inflammatory bowel disease), central nervous system (CNS) disorders such as Parkinson's disease and Alzheimer's disease, headache, anxiety, multiple sclerosis, attenuation of morphine withdrawal, cardiovascular changes, oedema, chronic inflammatory diseases such as rheumatoid arthritis, asthma/bronchial hyperreactivity and other respiratory diseases including allergic rhinitis, inflammatory diseases of the gut including ulcerative colitis and Crohn's disease, ocular injury and ocular inflammatory diseases. The background even mentions motion sickness and vomiting, but fails to call out nausea specifically.

Accordingly, there is a need in the art for more effective treatments of nausea and vomiting, particularly nausea and vomiting emanating from chemotherapy, radiotherapy and surgery. In addition, given the prolonged incidence of nausea and vomiting induced by these emetic events, there is a need for treating such nausea and vomiting for a prolonged period of time. Further, there is a need for the development of dosage forms to reduce drug-drug

interaction, improve stability, and potentiate effects of each component of the combined dosage forms.

OBJECTS OF THE INVENTION

Accordingly, it is an object of the invention to provide new methods for treating or preventing nausea and vomiting using an NK_1 antagonist, particularly netupitant.

It is another object of the invention to provide methods for treating or preventing nausea and vomiting in patients undergoing chemotherapy, radiotherapy, or surgery.

Still another object of the invention is to augment existing treatments for CINV, RINV or PONV by steroids and 5-HT_3 antagonists, and thereby provide additional protection against both nausea and vomiting, especially during the acute and delayed phases.

Another object of the invention is to provide a single combined dose of netupitant and a 5-HT_3 antagonist and to the use of that single dose without further dosing, for the treatment of nausea and vomiting during the acute and delayed phases of CINV, RINV or PONV.

It is another object to provide novel methods to treat nausea, vomiting, and other undesirable effects from moderately emetogenic and highly emetogenic chemotherapy ("MEC and HEC"), especially HEC, during the acute and delayed phases following such treatments.

It is another object to provide novel dosage forms to reduce drug-drug interaction, improve stability, enhance bioavailability and potentiate therapeutic effect of each component of the combined dosage forms comprising netupitant and/or 5-HT_3 antagonist and/or dexamethasone, in treating or preventing nausea and vomiting.

SUMMARY OF THE INVENTION

After extensive testing into the clinical effects of netupitant, it has unexpectedly been discovered that netupitant is active against nausea, and that a single dose of netupitant is able to treat nausea and vomiting in response to highly and moderately emetogenic chemotherapy for five consecutive days. It has also been discovered, quite unexpectedly, that netupitant exhibits unique binding habits to NK_1 receptors in the brain. In particular, it has been discovered that netupitant binds to NK_1 receptors in the striatum in a long-lasting manner, and that less than 20 or 30% of netupitant is released from striatum NK_1 receptors even ninety-six hours after administration. This is in stark contrast to aprepitant, in which receptor binding drops swiftly

over time, and must be dosed repeatedly if emesis control is desired throughout the delayed phase; and which shows no meaningful effect against nausea.

These discoveries have led to the development of a unique dosing regimen to treat nausea during the first day after an emesis-inducing event, in addition to the second, third, fourth and fifth days after such induction. Therefore, in one embodiment the invention provides a method of treating nausea and vomiting for a period of five consecutive days in a patient in need thereof, comprising administering to said patient netupitant or a pharmaceutically acceptable salt thereof in an amount which is therapeutically effective against nausea and vomiting during the acute and delayed phases, and which is effective to enter the systemic circulation, cross the blood brain barrier and occupy at least 70% of NK_1 receptors in the striatum seventy-two hours after said administration.

In another embodiment, the netupitant is combined with other anti-emetic agents, including a 5-HT_3 antagonist such as palonosetron and a corticosteroid such as dexamethasone, in a manner that results in even greater efficacy against nausea. It has been discovered that palonosetron is much more effective in combinations with netupitant than it is in combination with aprepitant, as reported by Grunberg et al., Support Cancer Care (2009) 17:589-594. In addition, palonosetron shows an improved pharmacokinetic profile (e.g., better bioavailability) when palonosetron is in combination with netupitant as opposed to palonosetron in single dose administration. Based on these discoveries, solid oral dosage forms have been developed that combine netupitant or another NK1 antagonist and palonosetron for the treatment of acute and delayed emesis.

It has also been discovered that netupitant potentiates the effect of dexamethasone, such that the dexamethasone is effective even when administered at sub-therapeutic doses (i.e. doses at which the dexamethasone would be ineffective if administered by itself). Therefore, in another embodiment the invention provides a combination therapy for treating nausea and vomiting for five consecutive days in a patient in need thereof, consisting essentially of:

- Day 1 netupitant -- administering to said patient on day one netupinant or a pharmaceutically acceptable salt thereof, in an amount which is therapeutically effective against nausea and vomiting during the acute and delayed phases, and which is effective to enter the systemic circulation, cross the blood brain barrier and occupy at least 70% of NK_1 receptors in the striatum seventy-two hours after said administration;

- Day 1 palonosetron -- administering to said patient on day one a therapeutically effective amount of a 5-HT_3 antagonist (preferably palonosetron) effective to treat said nausea and vomiting during the acute and delayed phases;
- Day 1 dexamethasone -- administering to said patient on day one a first dose of dexamethasone which is ineffective against nausea and vomiting when administered alone, but effective against nausea and vomiting when administered in combination with said netupitant and palonosetron, wherein said first dose comprises from 50 to 70% of a minimum effective dose when administered alone; and
- Days 2-5 dexamethasone — when the patient is undergoing highly emetogenic chemotherapy, administering to said patient, on days two, three and four, a second dose of dexamethasone which is ineffective against nausea and vomiting when administered alone, but effective against nausea and vomiting when administered in combination with said netupitant, wherein said second dose comprises from 40 to 60% of a minimum effective dose when administered alone on days two, three and four.

The dosage forms are extremely versatile and stable owing to their unique design and formulation. This versatility and stability is accomplished by formulating the NK1 antagonist and palonosetron in separate dosage forms and combining the dosage forms in one capsule. Thus, for example, the palonosetron can be formulated in a small gel-cap at a dose of around 0.5 mg, and the netupitant or other NK1 antagonist formulated in a tablet at a dose of about 100 to 150 mg. A capsule can then be filled with one or more palonosetron gel-caps and one or more netupitant (or other NK1 antagonist) tablets, depending on the therapeutic objective for the product. Because the palonosetron and NK1 antagonist are in separate dosage units, they can be formulated without regard to the stability of the other, and without degradation to by-products, for instance (3S)-3-[(3aS)-1-oxo- 2,3,3a,4,5,6-hexahydro-1*H*-benzo[*de*] isoquinoline-2-y1]-1-azoniabicyclo[2.2.2]octan-1-olate, a degradation by-product of palonosetron. As a result, the presently discovered dosage forms offer advantages, such as, reducing drug-drug interaction, improving stability, and potentiating effects of each component of the dosage forms in treating or preventing emesis.

Thus, in one embodiment the invention provides an orally administered dosage form comprising a combination of palonosetron and an NK1 antagonist (preferably netupitant), or a pharmaceutically acceptable salt or prodrug thereof.

In another embodiment the invention provides an orally administered capsule dosage form comprising (a) an outer shell; (b) one or more tablets housed within said outer shell, each comprising an NK1 antagonist (preferably netupitant) or a pharmaceutically acceptable salt or prodrug thereof and one or more pharmaceutically acceptable excipients; and (c) one or more soft-gel capsules housed within the outer shell, each comprising palonosetron or a pharmaceutically acceptable ester or prodrug thereof and one or more pharmaceutically acceptable excipients; wherein said dosage form comprises (3S)-3-[(3aS)-1-oxo- 2,3,3a,4,5,6-hexahydro-1*H*-benzo [*de*] isoquinoline-2-y1]-1-azoniabicyclo[2.2.2]octan-l-olate in an amount that does not exceed 3 wt.%.

In still other embodiments the invention provides methods of treating acute and delayed-onset emesis by administering the dosage forms of the present invention to a human in need thereof, preferably shortly before the emesis inducing event.

Additional embodiments and advantages of the invention will be set forth in part in the description which follows, and in part will be obvious from the description, or may be learned by practice of the invention. The embodiments and advantages of the invention will be realized and attained by means of the elements and combinations particularly pointed out in the appended claims. It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as claimed.

BRIEF DESCRIPTION OF THE DRAWINGS

The accompanying drawings, which are incorporated in and constitute a part of this specification, illustrate several embodiments of the invention and together with the description, serve to explain the principles of the invention.

FIG. 1 depicts a capsule containing one soft-gel capsule of palonosetron and three tablets of netupitant.

FIG. 2 is a two dimensional graph plotting the pharmacokinetic profile of netupitant in humans following oral administration of netupitant alone and netupitant together with palonosetron.

FIG. 3 is a two dimensional graph plotting the pharmacokinetic profile of palonosetron in humans following oral administration of palonosetron alone and palonosetron together with netupitant.

FIG. 4 is a two dimensional graph plotting mean plasma concentrations of dexamethasone over time following administration with and without netupitant.

FIG. 5 contains two bar graphs that depict the average NK_1 receptor occupancy at 6, 24, 48, 72 and 96 hours after a single oral dose of 100, 300 and 450 mg. netupitant (N=2 for each dose) in striatum and occipital cortex, as measured using positron emission topography.

DETAILED DESCRIPTION OF THE INVENTION

The present invention may be understood more readily by reference to the following definitions and detailed description of preferred embodiments of the invention and the non-limiting Examples included therein.

Definitions and Use of Terms

When the singular forms "a," "an" and "the" or like terms are used herein, they will be understood to include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a pharmaceutical carrier" includes mixtures of two or more such carriers, and the like. The word "or" or like terms as used herein means any one member of a particular list and also includes any combination of members of that list.

When used herein the term "about" or "ca." will compensate for variability allowed for in the pharmaceutical industry and inherent in pharmaceutical products, such as differences in product strength and bioavailability due to manufacturing variations and time-induced product degradation. The term allows for any variation which in the practice of pharmaceuticals would allow the product being evaluated to be considered pharmaceutically equivalent or bioequivalent, or both if the context requires, to the recited strength of a claimed product.

Throughout the description and claims of this specification, the word "comprise" and variations of the word, such as "comprising" and "comprises," means "including but not limited to," and is not intended to exclude, for example, other additives, components, integers or steps.

As used herein, the term "Pharmaceutically acceptable" means that which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically

nor otherwise undesirable and includes that which is acceptable for veterinary use as well as human pharmaceutical use. In addition, the term "pharmaceutically acceptable salt" refers to a salt of a compound to be administered prepared from pharmaceutically acceptable non-toxic acids. Examples of suitable inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, sulfuric, and phosphoric. Suitable organic acids may be selected from aliphatic, aromatic, carboxylic and sulfonic classes of organic acids, examples of which are formic, acetic, propionic, succinic, camphorsulfonic, citric, fumaric, gluconic, isethionic, lactic, malic, mucic, tartaric, para-toluenesulfonic, glycolic, glucuronic, maleic, furoic, glutamic, benzoic, anthranilic, salicylic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, pantothenic, benzenesulfonic (besylate), stearic, sulfanilic, alginic, galacturonic, and the like.

Pharmaceutically acceptable salts of palonosetron include palonosetron hydrochloride. Pharmaceutically acceptable pro-drugs of netupitant include those described in U.S. Patent Nos. 6,593,472, 6,747,026 and 6,806,370, including the N-oxide of netupitant. The contents of these publications are incorporated herein by reference. When a molecule is referred to herein in its base or salt form, it will be understand also to encompass other pharmaceutically acceptable salt forms of the molecule.

As used herein, "therapeutically effective amount" refers to an amount sufficient to elicit the desired biological response. The therapeutically effective amount or dose will depend on the age, sex and weight of the patient, and the current medical condition of the patient. The skilled artisan will be able to determine appropriate dosages depending on these and other factors in addition to the present disclosure.

The minimum effective dose of dexamethasone, when used to treat CINV induced by highly emetogenic chemotherapy, has been demonstrated to be 20 mg. administered orally or by injection on day one, and sixteen mg. administered orally or by injection on days two, three and four. Jordan *et al.,* THE ONCOLOGIST, Vol. 12, No. 9, 1143-1150, September 2007. When used to treat CINV induced by moderately emetogenic chemotherapy, the minimum effective dose of dexamethasone is 20 mg. administered orally or by injection on day one, and zero mg. on days two, three and four.

The terms "treating" and "treatment," when used herein, refer to the medical management of a patient with the intent to cure, ameliorate, stabilize, or prevent a disease, pathological condition, or disorder. This term includes active treatment, that is, treatment directed specifically toward the improvement of a disease, pathological condition, or disorder,

and also includes causal treatment, that is, treatment directed toward removal of the cause of the associated disease, pathological condition, or disorder. In addition, this term includes palliative treatment, that is, treatment designed for the relief of symptoms rather than the curing of the disease, pathological condition, or disorder; preventative treatment, that is, treatment directed to minimizing or partially or completely inhibiting the development of the associated disease, pathological condition, or disorder; and supportive treatment, that is, treatment employed to supplement another specific therapy directed toward the improvement of the associated disease, pathological condition, or disorder.

As used herein, the term "significantly" refers to a level of statistical significance. The level of statistical significant can be, for example, of at least $p<0.05$, of at least $p<0.01$, of at least $p<0.005$, or of at least $p<0.001$. Unless otherwise specified, the level of statistical significance is $p<0.05$. When a measurable result or effect is expressed or identified herein, it will be understood that the result or effect is evaluated based upon its statistical significance relative to a baseline. In like manner, when a treatment is described herein, it will be understood that the treatment shows efficacy to a degree of statistical significance.

5-HT_3 antagonists include the various setrons such as, for example, palonosetron, ondansetron, dolasetron, tropisetron, and granisetron, and their pharmaceutically acceptable salts. A preferred 5-HT_3 antagonist is palonosetron, especially its hydrochloride salt.

"Highly emetogenic chemotherapy" refers to chemotherapy having a high degree of emetogenic potential, and includes chemotherapy based on carmustine, cisplatin, cyclophosphamide > 1500 mg/m^2, dacarbazine, dactinomycin, mechlorethamine, and streptozotocin.

"Moderately emetogenic chemotherapy" refers to chemotherapy having a moderate degree of emetogenic potential, and includes chemotherapy based on carboplatin, cyclophosphamide < 1500 mg/m^2, cytarabine > 1 mg/m^2, daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, and oxaliplatin.

Acute emesis refers to the first twenty-four hour period following an emesis-inducing event. Delayed emesis refers to the second, third, fourth and fifth twenty-four hour periods following an emesis-inducing event. When a treatment is said to be effective during the delayed phase, it will be understood to mean that the effectiveness of the treatment is statistically significant during the entire delayed phase, regardless of whether the treatment is effective during any particular twenty-four hour period of the delayed phase. It will also be

understood that the method can be defined based upon its effectiveness during any one of the twenty-four hour periods of the delayed phase. Thus, unless otherwise specified, any of the methods of treating nausea and/or vomiting during the delayed phases, as described herein, could also be practiced to treat nausea and/or vomiting during the second, third, fourth or fifth twenty-four hour periods following an emesis inducing event, or an combination thereof.

When ranges are given by specifying the lower end of a range separately from the upper end of the range, it will be understood that the range can be defined by selectively combining any one of the lower end variables with any one of the upper end variables that is mathematically possible.

Methods of Treatment

As noted above, the invention is premised on several unique discoveries, and provides the following independent methods that can be practiced according to the present invention, including:

In a first principal embodiment, the invention provides a method of treating nausea and vomiting for a period of five consecutive days in a patient in need thereof, comprising administering to said patient netupitant or a pharmaceutically acceptable salt thereof in an amount which is therapeutically effective to treat nausea and vomiting during the acute and delayed phases, which enters the systemic circulation, crosses the blood brain barrier and occupies at least 70% of NK_1 receptors in the striatum seventy-two hours after said administration.

In a second principal embodiment, the invention provides a combination therapy for treating nausea and vomiting for five consecutive days in a patient in need thereof, comprising:

(i) administering to said patient on day one netupitant or a pharmaceutically acceptable salt thereof, in an amount which is therapeutically effective to treat nausea and vomiting during the acute and delayed phases, which enters the systemic circulation, crosses the blood brain barrier and occupies at least 70% of NK_1 receptors in the striatum seventy-two hours after said administration;

(ii) administering to said patient on day one a therapeutically effective amount of a 5-HT_3 antagonist (preferably palonosetron, more preferably 0.5 mg. of oral palonosetron as

palonosetron hydrochloride) effective to treat said nausea and vomiting during the acute and delayed phases;

(iii) administering to said patient on day one a first dose of dexamethasone which is ineffective against nausea and vomiting when administered alone, but effective against nausea and vomiting when administered in combination with said netupitant and palonosetron, wherein said first dose comprises from 50 to 70% of a minimum effective dose when administered alone; and

(iv) if the patient is undergoing highly emetogenic chemotherapy, administering to said patient, on days two, three and four, a second dose of dexamethasone which is ineffective against nausea and vomiting when administered alone, but effective against nausea and vomiting when administered in combination with said netupitant, wherein said second dose comprises from 40 to 60% of a minimum effective dose when administered alone on days two, three and four.

Various sub-embodiments are envisaged for these principal embodiments. For example, the netupitant can be administered as a free base or a pharmaceutically acceptable salt thereof, but is preferably administered as the free base. In addition, the netupitant is preferably administered in an amount ranging from about 50 to about 500 mg., from about 200 to about 400 mg., and preferably about 300 mg., based on the weight of the free base. A preferred route of administration for the netupitant is oral. In terms of binding to NK_1 receptors, the netupitant preferably binds to at least 80 or even 85% of NK_1 receptors in the striatum seventy-two hours after administration. As of ninety six hours after administration, the netupitant preferably binds less than 70, 60, 50 or even 40% of said NK_1 receptors.

The methods of the present invention are all effective at treating or preventing nausea and vomiting induced by numerous events, including chemotherapy induced nausea and vomiting ("CINV"), from moderately or highly emetogenic chemotherapy, radiation therapy induced nausea and vomiting ("RINV"), and post-operative nausea and vomiting ("PONV"). The method is preferably performed shortly before the emesis inducing event (i.e. no more than 1 or 2 hours before the event). The methods may be used to treat nausea and vomiting during the acute phase of emesis, or during the delayed phase.

The drugs specified by the individual embodiments may be administered by any suitable dosing regimen, as is well known in the art, but in a preferred embodiment the netupitant, 5-HT_3

antagonist and steroid are administered orally. A preferred oral dose of palonosetron ranges from about 0.075 to about 1.0 mg, or from about 0.25 to about 0.75 mg, but is preferably about 0.5 mg. A preferred oral dose of netupitant ranges from about 50 to 500 mg, or from about 200 to about 400 mg, but is preferably about 300 mg. A preferred dose of corticosteroid, preferably dexamethasone, is 12 mg administered orally or via injection on the first day of treatment, and 8 mg administered orally or via injection on the second, third and fourth days after said treatment.

It will be further understood that the netupitant can be administered in prodrug form, in which case the invention will provide a method of treatment by inducing plasma levels of netupitant, and in each case the plasma level of netupitant induced by the prodrug administration will correspond to the level attained by the administration of netupitant or its pharmaceutically acceptable salt, in the doses and routes of administration described herein.

Pharmaceutical Compositions

Various pharmaceutical compositions can be developed that make use of the combinations described herein. The composition can be administered by any appropriate route, for example, orally, parenterally, or intravenously, in liquid or solid form.

Preferred modes of administrations of the active compounds are injectable and/or oral. These compositions will generally include an inert diluent or an edible carrier. They may be enclosed in gelatin capsules (for oral use) or compressed into tablets (for oral or buccal use) or formulated into troches (for buccal use). For these purposes, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition.

Tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a gliding such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring. When the dosage unit form is a capsule, it can contain, in addition to material of the above type, a liquid carrier such as a fatty oil. In addition, dosage unit forms can contain various other materials which modify the physical form of the dosage unit, for example, coatings of sugar, shellac, or other enteric agents.

The compounds can be administered as a component of an elixir, suspension, syrup, wafer, orally disintegrating film, orally disintegrating tablet, chewing gum or the like. A syrup may contain, in addition to the active compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors.

Solutions or suspensions used for injection can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride, mannitol and dextrose. An injectable preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

Combined Oral Dosage Forms

As discussed above, the invention provides versatile combined oral dosage forms of palonosetron and an NK1 antagonist that can be readily modified depending on the therapeutic objective, and that do not present issues of stability and degradation. In a preferred embodiment, the invention provides a capsule for oral administration made from a hard outer shell that houses one or more NK1 antagonist tablets and one or more palonosetron soft-gel capsules. The finished capsule and the tablet(s) and soft-gel capsule(s) housed within the capsule shell are all preferably formulated as immediate release dosage forms. Netupitant and casopitant, and their pharmaceutically acceptable salts, are particularly preferred NK_1 antagonists for the combined oral dosage forms of this invention.

While the NK1 antagonist is preferably formulated in a solid tablet, it will be understood that it can be formulated in any solid form that is suitable for oral administration including, for example, a tablet or capsule (hard or soft-gel). In a preferred embodiment, the NK1 antagonist is formulated in a tablet. The number of NK1 antagonist units contained within the combined dosage form can be, for example, from 1 to 10, 1 to 5, or 1 to 3. The netupitant units within the combined dosage form can provide anywhere from 50 to 500 mg of netupitant on an aggregate basis, preferably from 100 to 350 mg. Each netupitant unit preferably comprises from 50 to 200

mg of netupitant, more preferably 100 to 150 mg of netupitant, and most preferably 100 or 150 mg of netupitant.

The palonosetron can also be formulated in any solid form that is suitable for oral administration, although it is preferably formulated as a soft-gel capsule. Non-limiting examples of suitable palonosetron soft-gel capsules are provided in PCT publication WO 2008/049552, the contents of which are hereby incorporated by reference. The number of palonosetron units within the combined dosage from can be, for example, from 1 to 5, from 1 to 3 or just 1. Each of the palonosetron units within the combined dosage form can provide anywhere from 0.01 to 5.0 mg palonosetron, preferably from 0.1 to 1.0 mg palonosetron on an aggregate basis. Each palonosetron unit will preferably comprise from 0.1 to 1.0 mg of palonosetron, most preferably about 0.25, 0.5, 0.75 or 1.0 mg of palonosetron.

Figure 1 illustrates an exemplary embodiment of a combined oral dosage form of palonosetron and netupitant. The dosage form 10 comprises a two piece hard outer shell that includes a body 20 and a cap 22. The dosage form 10 contains one palonosetron soft-gel capsule 30 (preferably containing 0.5 mg of palonosetron) and three netupitant tablets 40 (each preferably containing 100 mg of netupitant).

Hard Outer Shell

The hard outer shell of the present invention can be made of any pharmaceutically acceptable material that dissolves in gastric fluids. Preferred materials for the hard outer shell include, for example, gelatin, cellulose, starch, or hydroxypropyl methylcellulose (HPMC). In a particular embodiment of the invention, the hard outer shell has a maximum oxygen permeability. Preferably, the oxygen permeability is less about 1.0×10^{-3}, 5.0×10^{-4}, 1.0×10^{-4}, 5.0×10^{-5}, or even 2.0×10^{-5} ml·cm/(cm^2·24 hr. atm).

The hard outer shell can be a continuous structure. Alternatively, the hard outer shell can be a two-piece hard capsule.

Soft-Gel Capsule

The soft-gel capsule used for the palonosetron preferably comprises a soft outer shell and a liquid inner fill composition comprising palonosetron hydrochloride. Non-limiting examples of

suitable palonosetron soft-gel capsules are provided in PCT publication WO 2008/049552, the contents of which are hereby incorporated by reference.

The soft outer shell of the soft-gel capsule can contain any type of material that dissolves in gastric fluids. Preferred materials for the soft outer shell include, for example, gelatin, cellulose, starch, or hydroxypropyl methylcellulose (HPMC). The soft-gel capsule can further comprise shell excipients such as glycerin, sorbitol, and colorants/opacifers such as titanium dioxide. The soft-gel capsule can further include solvents such as purified water. In particular embodiments of the invention, the outer shell has a maximum oxygen permeability, preferably of no more than 1.0×10^{-3}, 5.0×10^{-4}, 1.0×10^{-4}, 5.0×10^{-5}, or even 2.0×10^{-5} ml·cm/(cm^2·24 hr. atm). Suitable soft-gel capsules include the 1.5-oval gelatine capsule shell manufactured by Catalent Pharma Solutions.

The liquid fill is preferably composed predominantly of one or more lipophilic components in an amount of from 50 wt.% to 99 wt.%, preferably from 75 wt.% to 98 wt.%. Preferred lipophilic components include, for example, mono- and di-glycerides of fatty acids, especially including the mono- and di-glycerides of capryl/capric acid. The liquid fill may also contain glycerin, preferably in an amount of from 1 to 15 wt.%, more preferably from 2 to 10 wt.%. In one preferred embodiment, both the shell and the inner fill composition comprise glycerin. In another preferred embodiment, the liquid fill comprises about 0.25, 0.50, 0.75 mg., or more of palonosetron as palonosetron hydrochloride.

The fill composition may comprise various means to facilitate the transition of palonosetron from the dosage form to the gastrointestinal fluids of the GI tract, so that the palonosetron may be more readily absorbed into the bloodstream. For example, the liquid fill composition may contain a surfactant, optimally in an amount of from 0.1 wt.% to 6 wt.%, from 0.5 wt.% to 5 wt.%, or from 1.0 wt.% to 3.0 wt.%. The liquid fill composition preferably comprises greater than 0.1, 0.5, or 1.0 wt.% of surfactant, and less than 10, 8, 5, 4, or even 4 wt.% of surfactant. A particularly preferred surfactant is polyglyceryl oleate.

Alternatively or in addition, the transitioning means for a liquid filled capsule may comprise water that forms a single phase or microemulsion with the other liquid ingredients in the excipient base. The liquid fill composition preferably comprises from 0.05 wt.% to 30 wt.% water, from 1 wt.% to 20 wt.% water, or from 2 wt.% to10 wt.% water. The liquid fill preferably comprises greater than 0.1, 0.5 or 1.0 wt.% water, and less than 20, 15, 10, 8 or 5 wt.% water.

The active agent, which is preferably palonosetron hydrochloride, is preferably present in the fill composition in an amount ranging from 0.01 to 10.0 wt.%, from 0.05 to 5.0 wt.%, or from 0.1 wt.% to 2.0 wt.%. Alternatively, particularly stable formulations have been found where the concentration of palonosetron exceeds 0.3%, preferably at a concentration no greater than 1 wt.%.

Tablet

The tablets of the present invention can include from 20 to 95 wt.% of NK1 antagonist (preferably netupitant), and preferably comprises from 60 to 80 wt.% of netupitant. In addition, the tablets can contain diluents, disintegrants, surfactants, binders, glidants, and/or lubricants. In a particular embodiment, the tablet comprises from 5 to 25 wt.% of microcrystalline cellulose. The microcrystalline cellulose can function as a diluent and disintegrant, and preferably comprises 15 wt.% of the tablet. Another suitable disintegrant is sodium croscaramellose, which can be present in the tablet in an amount of from 1 to 5 wt.%, preferably 2 wt.%.

A suitable binder for use in the tablet is polyvinylpyrrolidone, which can be present in the tablet in an amount from 1 to 10 wt.% of the tablet, and preferably 5 wt.%. A suitable glidant for use in the tablet is colloidal silicon dioxide, which can be present in the tablet in an amount of 2 wt.%. Suitable lubricants for use in the tablet include sodium stearyl fumarate and magnesium stearate, which can be present in the tablet in an amount of 0.7 wt.% and 0.35 wt.%, respectively.

Application of The Combined Oral Dosage Forms

The invention further provides a method of treating emesis comprising orally administering to a patient suffering from emesis, or at risk for suffering emesis, a dosage form of the present invention. In still further embodiments, the invention provides methods of treating emesis by administering one or more of the dosage forms described herein. The dosage form is preferably administered shortly before the emesis inducing event (i.e. no more than 2 hours before the event). The emesis may be acute phase emesis (i.e. emesis experienced within about 24 hours of an emesis inducing event), or delayed emesis (i.e. emesis experienced after the acute phase, but within seven, six, five or four days of an emesis inducing event). The emesis may constitute chemotherapy induced nausea and vomiting ("CINV"), from moderately

or highly emetogenic chemotherapy, radiation therapy induced nausea and vomiting ("RINV"), or postoperative nausea and vomiting ("PONV").

EXAMPLES

The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how the compounds claimed herein are made and evaluated, and are intended to be purely exemplary of the invention and are not intended to limit the scope of what the inventors regard as their invention. Efforts have been made to ensure accuracy with respect to numbers (e.g., amounts, temperature, etc.) but some errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, temperature is in °C or is at room temperature, and pressure is at or near atmospheric.

EXAMPLE 1 — PREPARATION OF ORAL DOSAGE FORM

In a preferred embodiment the combination is administered in a capsule oral dosage form, wherein the capsule houses one or more soft-gel capsules for the palonosetron and one or more hard tablets for the netupitant. Table 1 below describes a representative formulation for a soft-gel capsule containing 0.5 mg of palonosetron, suitable for inclusion in such a hard outer shell.

TABLE 1: REPRESENTATIVE SOFT-GEL FORMULATION

Ingredient	Approximate Amount	Function
Fill Solution		
Palonosetron HC1	0.56[1]	Active
Mono- and di-glycerides of	62.19	Solvent vehicle
Glycerin, anhydrous, USP/Ph Eur	3.37	Plasticizer
Polyglyceryl oleate (Plurol Oleique CC 497)	0.87	Surfactant
Purified water, USP/Ph Eur	2.94	Co-solvent
Butylated hydroxyanisole (BHA), NF/Ph Eur	0.07	Antioxidant
Nitrogen	-	
Theoretical fill weight	70.00 mg	
Gelatine Capsule Shell, 1.5-oval (Catalent Pharma Solutions)[2]		
Gelatine (type 195), NF/Ph Eur	-	Shell
Sorbitol Special/Glycerin Blend 50/50	-	Plasticizer
Titanium dioxide, USP/Ph Eur	-	Colorant/Opacifier
Purified water, USP/Ph Eur	-	Solvent

[1]Corresponds to 0.50 mg. free base

[2]Quantitative composition of capsule shell is proprietary to Catalent Pharma Solutions

Table 2 below describes a representative formulation for a tablet containing 100 mg. of netupitant, suitable for inclusion in a hard shell.

TABLE 2: REPRESENTATIVE TABLET FORMULATION

Ingredient	Approximate Amount (mg/Tablet)	Function
Netupitant, milled	100	Active
Microcrystalline cellulose pH 101	20.5	Diluent and disintegrant
Sucrose Lauric Acid Esters	10.0	Surfactant
Polyvinilpyrrolidone K30	7.0	Binder
Sodium croscaramellose	3.0	Disintegrant
Colloidal Silicon Dioxide	3.0	Glidant
Sodium Stearyl Fumarate	1.0	Lubricant
Magnesium Stearate	0.5	Lubricant
Total weight	145 mg	

EXAMPLE 2 — PHARMACOKINETICS OF COMBINED DOSAGE FORM

Objective

The effects of palonosetron on the pharmacokinetics (PK) of netupitant and the effects of netupitant on the PK of palonosetron were examined in healthy volunteers.

Methods

A randomized, open, 3-way crossover study was conducted. Each subject participated in 3 treatment periods, each lasting approximately 12 days (Day -1 to Day 11). The treatment periods were separated by wash-out periods of no less than 14 days (between Day 1 of any 2 consecutive treatment periods).

The following treatments were investigated:

Treatment A: oral netupitant 450 mg. administered as single dose of three 150 mg. capsules.

Treatment B: oral palonosetron 0.75 mg. and oral netupitant 450 mg. administered simultaneously as three capsules of 150 mg. netupitant followed by 1 capsule of 0.75 mg. palonosetron.

Treatment C: oral palonosetron 0.75 mg. administered as single dose as one 0.75 mg. capsule.

Doses were administered under fasting conditions. Subjects fasted over-night for approximately 10 hours. Water, however, was permitted up to 1 hour pre-dose. Food intake was permitted 4 hours post-dose, and water was allowed ad libitum 1 hour post-dose.

Doses were administered with the subject in an upright position. The subjects remained in an upright position for 4 hours post-dose. The capsules were swallowed whole with 250 mL of room-temperature tap water. Repeated PK blood sampling (for netupitant and/or palonosetron) was performed.

Results

The primary PK variables assessed for netupitant and palonosetron were the maximum plasma concentration observed (C_{max}), the area under the plasma concentration versus time curve from time zero to the last quantifiable sampling time point (t) (AUC_{0-t}), and the area under the plasma concentration versus time curve from time zero to infinity (AUC_{0-inf}). The secondary PK variables assessed were the terminal elimination half-life ($t_{½, z}$), and the time at which the maximum plasma concentration was observed (t_{max}). Results are depicted in below Tables 3 and 4, as well as Figures 2 and 3.

Table 3: Summary of Netupitant Pharmacokinetic Parameters

Parameter	Netupitant 450 mg	Palonosetron 0.75 mg + Netupitant 450 mg
AUC_{0-t} [h*µg/L]	22808 (7270)	22775 (10064)
AUC_{0-inf} [h*µg/L]	25927 (10156)	26241 (13219)
C_{max} [µg/L]	650.2 (257.8)	659.7 (325.7)
t_{max} (h)	4.50 (3.00 ; 24.00)	4.50 (3.00 ; 23.95)
$t_{½,z}$ (h)	71.81 (37.10 ; 261.61)	78.31 (50.17 ; 196.13)

Mean and SD are shown, except for t_{max} and $t_{½}$, where median and range are shown.

As can be seen in Table 4 below, palonosetron shows a better pharmacokinetic profile when combined with Netupitant as opposed to administered as a single dose of palonosetron, for example, the greater AUC, the larger $C_{max,}$ the shorter t_{max}, (the median t_{max} was 0.5 hour shorter after administration of palonosetron in combination with netupitant), and the longer $t_{½,z}$.

Table 4: Summary of Palonosetron Pharmacokinetic Parameters

Parameter	Palonosetron 0.75 mg	Palonosetron 0.75 mg +
AUC_{0-t} [h*µg/L]	67415 (19554)	74230 (24866)
AUC_{0-inf} [h*µg/L]	70813 (20415)	77254 (25402)
C_{max} [µg/L]	1638.4 (415.5)	1863.1 (487.1)
t_{max} (h)	5.02 (4.00 ; 8.00)	4.50 (3.00 ; 6.02)
$t_{½,z}$ (h)	34.73 (19.61 ; 70.46)	36.91 (20.23 ; 56.08)

Mean and SD are shown, except for t_{max} and $t_{½}$, where median and range are shown.

EXAMPLE 3: NETUPITANT + DEXAMETHASONE DRUG INTERACTION STUDY

The effect of netupitant on orally administered dexamethasone pharmacokinetics was evaluated in this study. This was a randomized, open, 3-period crossover study utilizing an incomplete Latin Square design where subjects were given dexamethasone alone, or oral

Netupitant 100 mg., 300 mg. or 450 mg. each given with dexamethasone. Netupitant was given orally on Day 1 only. The dexamethasone regimen for each treatment was 20 mg. orally Day 1, followed by 8 mg. orally every 12 hours from Day 2 through Day 4. Nineteen subjects (12 male and 7 female) completed the study (i.e., all 3 treatment periods).

Mean plasma concentrations of dexamethasone were higher when dexamethasone was co-administered with netupitant (Figure 4). The increase appeared to be dependant on the netupitant exposure.

The AUC_{0-24} (Day 1) of dexamethasone increased 1.5, 1.7 and 1.8-fold with co-administration of 100, 300 and 450 mg. netupitant, respectively. The AUC_{24-36} (Day 2) of dexamethasone increased 2.1, 2.4 and 2.6-fold and AUC_{84-108} and AUC_{84-inf} (Day 4) increased 1.7, 2.4 and 2.7-fold, with co-administration of 100, 300 and 450 mg. netupitant, respectively. Dexamethasone C_{max} on Day 1 was only slightly affected by co-administration of netupitant (1.1-fold increase during co-administration with 100 and 300 mg. netupitant, respectively, and 1.2-fold increase during co-administration with 450 mg. netupitant). C_{max} on Day 2 and Day 4 was increased approximately 1.7-fold in subjects administered netupitant. Dexamethasone C_{min} on Days 2-4 was increased approximately 2.8, 4.3 and 4.6-fold with co-administration of 100, 300 and 450 mg. netupitant, respectively. This clearly shows that the co-administration of netupitant and dexamethasone enhances the bioavailability of dexamethasone and provides a better therapeutic window of dexamethasone.

EXAMPLE 4: NETUPITANT PET RECEPTOR OCCUPANCY STUDY

This was a randomized, open-label, positron emission tomography (PET) study using 11C-GR205171 as tracer in 6 healthy male volunteers (2 per dose level) receiving single doses of netupitant (100, 300 or 450 mg) to investigate the degree of occupancy of NK_1 receptors in human brain, and to determine the relationship between plasma concentration of netupitant and NK_1 receptor occupancy (RO).

The anticipated high NK_1-RO (90% or higher) close to the expected C_{max} (6 hours post dose) was reached for striatum, occipital cortex, frontal cortex and anterior cingulate in 3 of 6 subjects of whom 1 received 300 mg. and 2 received 450 mg. of netupitant as a single oral dose.

All doses showed a relatively long duration of blockade of NK_1 receptors and the decline over time was dose dependent. In the 100 mg. dose group, 4 of 6 regions still had a mean NK_1-RO over 70% at 96 hours post dose. In the highest dose group (450 mg), 5 of 6 regions had a mean NK_1-RO of 80% or higher at 96 hours post dose. A comparison of the results for the dose groups (100 mg., 300 mg. and 450 mg) showed a consistent but small increase in NK_1-RO_s with increasing netupitant dose. (Figure 5)

EXAMPLE 5: CLINICAL EFFICACY STUDY

A phase 2 trial evaluated three single doses of netupitant combined with palonosetron and dexamethasone compared to palonosetron alone and dexamethasone to obtain dose ranging information for netupitant used with oral palonosetron in the CINV patient population.

The objective of the study was to compare the efficacy and safety of three single oral doses of netupitant combined with oral palonosetron and given with dexamethasone, versus oral palonosetron-alone given with dexamethasone (without netupitant) for the prevention of highly emetogenic chemotherapy (HEC)-induced nausea and vomiting. The FDA-approved oral aprepitant regimen given with IV ondansetron and dexamethasone was included in the study as an active comparator for exploratory purposes. The FDA-approved oral palonosetron 0.5 mg. dose was used in each applicable treatment group in this study.

This was a multicenter, randomized, double-blind, double-dummy, parallel group, stratified study. Eligible patients were randomized (stratified by gender) to one of the following treatment groups:

Group 1 — 0.5 mg. oral palonosetron on Day 1 (with an oral dexamethasone standard regimen: 20 mg. on Day 1 and 8 mg. BID from Day 2 through Day 4)

Group 2 — 100 mg. oral netupitant plus 0.5 mg. oral palonosetron on Day 1 (with an oral dexamethasone adjusted regimen*: 12 mg. on Day 1 and 8 mg. daily from Day 2 through Day 4)

Group 3 — 200 mg. oral netupitant plus 0.5 mg. oral palonosetron on Day 1 (with an oral dexamethasone adjusted regimen*: 12 mg. on Day 1 and 8 mg. daily from Day 2 to Day 4)

Group 4 — 300 mg. oral netupitant plus 0.5 mg. oral palonosetron on Day 1 (with dexamethasone adjusted regimen*: 12 mg. on Day 1 and 8 mg. daily from Day 2 to Day 4)

Group 5 — 125 mg. oral aprepitant plus IV ondansetron 32 mg. (both on Day 1) then 80 mg. oral aprepitant on Day 2 and Day 3, (all with an oral dexamethasone adjusted regimen: 12 mg. on Day 1 and 8 mg. daily from Day 2 through Day 4)

In addition, a Group 6 was added to the analysis for comparative purposes, based on the results reported by Grunberg et al., Support Cancer Care (2009) 17:589-594:

Group 6 — 285 mg. oral aprepitant plus 20 mg. oral dexamethasone plus 0.2 mg. palonosetron i.v. (all on Day 1) then 80 mg. oral aprepitant

The primary efficacy endpoint was the complete response rate (defined as no emetic episodes, no rescue medication) within 120 hours after the start of the highly emetogenic chemotherapy administration. Secondary efficacy endpoints were:

- Complete response for the 0-24 hour interval (acute phase); and for the 25-120 hour interval (delayed phase);
- Complete protection (defined as no emesis, no rescue therapy, no significant nausea); Total control (defined as no emesis, no rescue therapy and no nausea); No nausea (maximum VAS <5 mm); No significant nausea (maximumVAS <25 mm); No rescue medication; No emesis. These endpoints were evaluated for the 0-120 hour interval (overall), acute and delayed phase.
- Time to first emetic episode, Time to first rescue medication, Time to treatment failure (based on time to the first emetic episode or time to the first rescue medication, whichever occurs first);
- Severity of nausea for the overall, acute and delayed phase; • Patient global satisfaction with anti-emetic therapy by means of VAS for each 24 hour interval.

Complete response rates are summarized in Table 5. The percent of patients with complete response over 0-120 hours after start of cisplatin administration was 76.5% in the palonosetron alone group and 87.4%, 87.6%, and 89.6% in the netupitant 100 mg., 200 mg., and 300 mg. groups, respectively. Differences from palonosetron-alone were greater than

10% (10.9% to 13.2%). All doses of netupitant were statistically superior to palonosetron alone (p-value=0.004 for the netupitant 300 mg. combination group).

TABLE 5: COMPLETE RESPONSE RATE FOR THE OVERALL, ACUTE AND DELAYED PHASE: MFAS Population

Efficacy endpoint	Palo alone (n=136)	Palo + Netu 100 mg (n=135)	Palo + Netu 200 mg (n=137)	Palo + Netu 300 mg (n=135)	Aprepitant Regimen (N=134)
CR, Overall Phase, 0-120h					
Percent of Patients	76.5	87.4	87.6	89.6	86.6
Difference from Palo alone (%)		10.9	11.1	13.2	10.1
p-value (*)		0.018	0.017	0.004	0.027
CR, Acute Phase, -24h					
Percent of Patients	89.7	93.3	92.7	98.5	94.8
Difference from Palo alone (%)		3.6	3.0	8.8	5.1
p-value (*)		0.278	0.383	0.007	0.114
CR, Delayed Phase, 25-120h					
Percent of Patients	80.1	90.4	91.2	90.4	88.8
Difference from Palo alone (%)		10.2	11.1	10.2	8.7
p-value (*)		0.018	0.010	0.018	0.043

(*) p-value from logistic regression analysis, aprepitant p-value from post-hoc logistic regression analysis.

Table 6 summarizes results for main secondary endpoints. In the overall phase, 76.5% of patients in the palonosetron-alone group did not experience emesis, while 87.4, 87.6, and 91.1% of patients did not experience emesis in the netupitant 100 mg., 200 mg. and 300 mg. combination groups, respectively ($p<0.05$ for all doses).

TABLE 6: SUMMARY OF SECONDARY EFFICACY RESULTS: PERCENT OF PATIENTS, MFAS POPULATION

Efficacy endpoint	Palo alone (n=136)	Palo + Netu 100 mg (n=135)	Palo + Netu 200 mg (n=137)	Palo + Netu 300 mg (n=135)	Aprepitant Regimen (N=134)	Palo+Aprep 285 mg (N=41)**
No Emesis						
Overall	76.5	87.4*	87.6*	91.1*	87.3	
Acute	89.7	93.3	92.7	98.5*	94.8	
Delayed	80.1	90.4*	91.2*	91.9*	89.6*	
No Rescue						
Overall	95.6	97.8	100	98.5	97.8	
Acute	97.8	99.3	100	100	100	
Delayed	97.1	97.8	100	98.5	97.8	
No Nausea						
Overall	50.7	54.8	62.0	61.5	58.2	32
Acute	75.0	72.6	77.4	80.0	77.6	59
Delayed	53.7	59.3	65.0	68.1*	60.4	41
No Significant Nausea						
Overall	79.4	80.0	86.1	89.6*	85.8	56
Acute	93.4	94.1	94.2	98.5*	94.0	79
Delayed	80.9	81.5	89.8*	90.4*	88.1	59
Total Control						
Overall	50.0	54.8	61.3	59.3	56.0	
Acute	71.3	71.9	76.6	80.0	74.6	
Delayed	52.2	59.3	65.0*	65.9*	58.2	
Complete						

Protection						
Overall	69.9	76.3	80.3*	83.0*	78.4	51
Acute	87.5	89.6	88.3	97.0*	89.6	76
Delayed	73.5	80.0	87.6*	84.4*	82.1	66

* p-value ,0.05 compared with palonosetron-alone; aprepitant comparisons p-values calculated by post-hoc analysis

** As reported by Grunberg et al., Support Cancer Care (2009) 17:589-594

EXAMPLE 7: COMPARATIVE RESULTS OF APREPITANT DOSING REGIMEN

The following Table 8 reports the results observed for an aprepitant dosing regimen, as described in the FDA approved prescribing information for aprepitant, which demonstrates, among other things, that aprepitant has no meaningful effect on nausea. Table 7 reports the dosing regimen:

TABLE 7

Treatment Regimen	Day 1	Day 2 to 4
Aprepitant	Aprepitant 125mg PO Dexamethasone 12 mg PO Ondansetron 32 mg I.V.	Aprepitant 80mg PO Daily (Days 2 and 3 only) Dexamethasone 8 mg PO Daily (morning)

TABLE 8

Percent of Patients Receiving Highly Emetogenic Chemotherapy Responding by Treatment Group and Phase for Study 1 – Cycle 1

ENDPOINTS	Aprepitant Regimen (N=260)† %	Standard Therapy (N=261)† %	p-Value
PRIMARY ENDPOINT			
Complete Response			
Overall‡	73	52	<0.001
OTHER PRESPECIFIED ENDPOINTS			
Complete Response			
Acute phase[1]	89	78	<0.001
Delayed Phase[2]	75	56	<0.001
Complete Protection			
Overall	63	49	0.001
Acute phase	85	75	NS*
Delayed phase	66	52	<0.001
No Emesis			
Overall	78	55	<0.001
Acute phase	90	79	0.001
Delayed phase	81	59	<0.001
No Nausea			
Overall	48	44	NS**
Delayed phase	51	48	NS**
No Significant Nausea			
Overall	73	66	NS**
Delayed phase	75	69	NS**

† N: Number of patients (older than 18 years of age) who received cisplatin, study drug, and had at least one post-treatment efficacy evaluation.

‡ Overall: 0 to 120 hours post-cisplatin treatment.

[1] Acute phase: 0 to 24 hours post-cisplatin treatment.

[2] Delayed phase: 25 to 120 hours post-cisplatin treatment.

* Not statistically significant when adjusted for multiple comparisons.

****

Throughout this application, various publications are referenced. The disclosures of these publications in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art to which this invention pertains. It will be apparent to those skilled in the art that various modifications and variations can be made in the present invention without departing from the scope or spirit of the invention. Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims.

NONPROVISIONAL APPLICATION FOR UNITED STATES PATENT

for

COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING

by:

Fabio Trento, a citizen of Italy residing at Via Alla Valle 20B I-22020 Pare (Como - Italy); Sergio Cantoreggi, a citizen of Switzerland residing at Via ai Ronchi, 37 CH-6943 Vezia Switzerland; Giorgia Rossi, a citizen of Italy residing at Via della Liberta, 1A - 1-22012 Cernobbio (Como - Italy); Roberta Cannella, a citizen of Italy, residing at Via Al Colle, 42 - 1-21100 Varese, Italy; Daniele Bonadeo, a citizen of Italy residing at Via Ronco Capo Caccia, 32 - I- 21030 Casalzuigno, Varese, Italy

COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. Application No. 14/069,970, filed November 1, 2013, which is a continuation of U.S. Application No. 13/077, 462, filed March 31, 2011, now U.S. Patent No. 8,623,826, issued January 7, 2014, which is a continuation of International Application No. PCT/IB2010/003106, filed November 18, 2010, which claims ~~benefit of~~ priority to U.S. Provisional Application No. 61/262,470, filed November 18, 2009, and ~~;~~ U.S. Provisional Application No. 61/382,709, filed September 14, 2010.~~; and International Patent Application No. PCT/US10/57192, filed November 19, 2010. Application Nos. 61/262,470 and 61/382,709 and PCT Application No. PCT/US10/57192~~ All of the above applications are hereby incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

The present invention relates to the use of centrally acting NK_1 antagonists to treat nausea and vomiting, particular nausea and vomiting induced by highly emetogenic chemotherapy, and to the treatment of such nausea and vomiting over multiple consecutive days. The present invention also relates to combined oral dosage forms of palonosetron and netupitant.

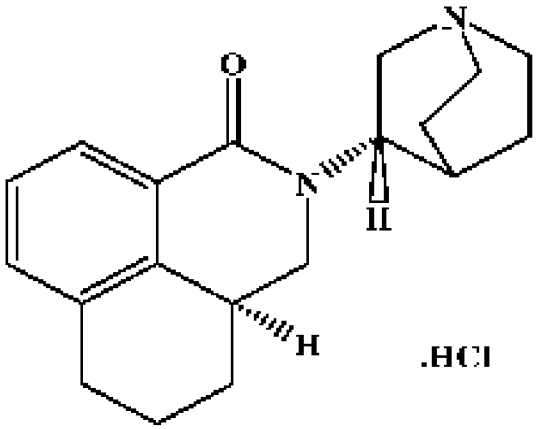
BACKGROUND OF THE INVENTION

With the development of the 5-HT_3 antagonist in the early 1990s, there emerged new strategies in the medical community to better control nausea and vomiting caused by various medical procedures, including chemotherapy (CINV), surgery (PONV), and radiation therapy (RINV). When added to steroids such as dexamethasone, several 5-HT_3 antagonists have been demonstrated to significantly improve the standard of life for patients undergoing emetogenic medical procedures. Examples of 5-HT_3 antagonists include ondansetron, marketed by GlaxoSmithKline, and palonosetron, developed by Helsinn Healthcare.

Palonosetron hydrochloride has recently emerged as a highly efficacious anti-nauseant and anti-emetic agent. See PCT publications WO 2004/045615 and 2004/073714 from Helsinn Healthcare. Palonosetron hydrochloride is sold in the United States as a sterile injectable liquid under the ALOXI® brand, in sterile unit dose vials containing 0.075 or 0.25 mg. of palonosetron

hydrochloride. Palonosetron hydrochloride also is also sold as an orally administered soft-gel dosage form containing 0.5 mg. of palonosetron hydrochloride.

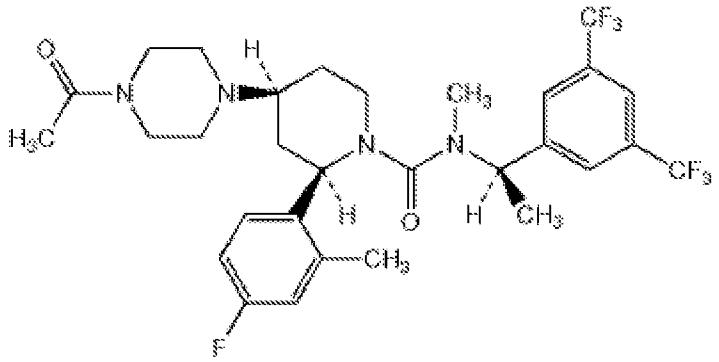
The official chemical name for palonosetron hydrochloride is (3aS)-2-[(S)-1-Azabicyclo [2.2.2] oct-3-y1]- 2,3,3a,4,5 ,6-hexahydro-l-oxo-l*H*beriz [*de*] isoquinoline hydrochloride (CAS No. 119904-90-4); its empirical formula is $C_{19}H_{24}N_2O \cdot HCl$, and its molecular weight is 332.87. The compound is represented by the following chemical structure:



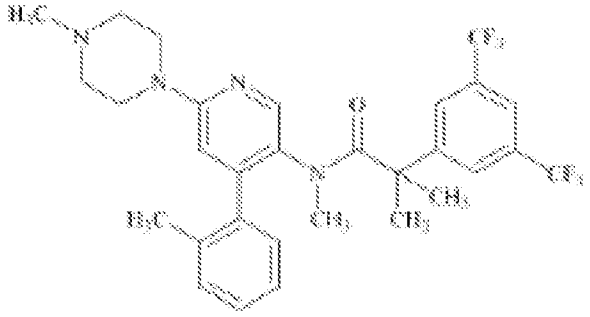
Methods of synthesizing palonosetron are described in U.S. Patent Nos. 5,202,333 and 5,510,486. Pharmaceutically acceptably dosage forms are described in PCT publications WO 2004/067005 and WO 2008/049552 from Helsinn Healthcare.

NK_1 antagonists have also recently emerged as a tool for combating nausea and vomiting from emetogenic medical procedures. Most recently, aprepitant was approved by the Food and Drug Administration ("FDA") for use in combination with other anti-emetic agents for the prevention of nausea and vomiting from moderately and highly emetogenic chemotherapy. However, it quickly became apparent that aprepitant's effect was limited principally to vomiting — not nausea — and that aprepitant did not provide as much benefit during the acute phase of CINV. When tested against nausea in humans, aprepitant was unable to induce a significant reduction in the incidence or severity of nausea following moderately or highly emetogenic chemotherapy when compared to a $5\text{-}HT_3$ antagonist alone. See FDA Approved Labeling for Emend®. Thus, while aprepitant is approved by FDA for the prevention of nausea and vomiting in humans, this indication is somewhat misleading because aprepitant did not reduce nausea in the clinical trials preformed for aprepitant more than nausea controlled by the other components of the anti-emetic regimen. In addition, the results reported in Grunberg *et al.,* SUPPORT CANCER CARE (2009) 17:589-594, from a combined treatment of aprepitant and palonosetron, were far from promising.

Merck & Co. markets aprepitant, as EMEND® in the United States. The product is approved in a capsule dosage form, and is marketed for the prevention of CINV (acute and delayed) in combination with other anti-emetic agents such as ondansetron and metoclopramide. The product reportedly has a terminal half-life of from 9 to 13 hours. While aprepitant has demonstrated some effect against nausea, its effects have been inconsistent. Casopitant is another NK_1 antagonist that has been tested against nausea and vomiting in humans. A clinical study of casopitant is discussed in *Therapeutics and Clinical Risk Management* 2009:5 pp375-384 to Ruhlmann et al. and *Drug Metabolism and Disposition,* vol.37, No. 8, 2009, pp.1635-1645 to Pellegatti et al. As reported by Ruhlmann *et al.* in THERAPEUTICS AND CLINICAL RISK MANAGEMENT, 2009:5 375-384, casopitant had no statistically significant effect against nausea when administered in response to moderately emetogenic chemotherapy, and even induced nausea as a side effect. Casopitant has the formula (2*R*,4*S*)-4-(4-acetytlpiperazin-l-y1)-*N*-{(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethy1}-2-(4-fluoro-2-methylpheny1)-*N*-methylpiperidine-l-carboxamide, and the below chemical structure:



Netupitant is another selective NK_1 receptor antagonist under development by Helsinn Healthcare, having the formula 2-[3,5-bis(trifluoromethyl)phenyl]-N,2-dimethyl-N-[4-(2-methylpheny1)-6-(4-methylpiperazin-l-y1)pyridin-3-yl]propanamide, or Benzeneacetamide, N,α,α-trimethyl-N-[4-(2-methylpheny1)-6-(4-methyl-l-piperaziny1)-3-pyridinyl]-3,5-bis(trifluoromethyl)-, and the below chemical structure:



Methods of synthesizing and formulating netupitant and its prodrugs are described in U.S. Patent Nos. 6,297,375, 6,719,996 and 6,593,472 to Hoffmann La Roche.

Other representative NK_1 antagonists include ZD4974 (developed by AstraZeneca), CGP49823 (developed by Ciba-Geigy), Lanepitant and LY686017 (developed by Eli Lilly), FK888 (developed by Fujisawa), Vofopitant, Vestipitant and Orvepitant (developed by GlaxoSmithKline), Befetupitant (developed by Hoffmann-La Roche), R116031 (developed by Janssen), L-733060 and L-736281 (developed by Merck), TKA731, NKP608 and DNK333 (developed by Novartis), CP-96345, CP-99994, CP-122721, CJ-17493, CJ-11974 and CJ-11972 (developed by Pfizer), RP67580 and Dapitant (developed by Rhone-Poulenc Rorer), Nolpitantium and SSR240600 (developed by Sanofi-Aventis), SCH388714 and Rolapitant (developed by Schering-Plough), TAK637 (developed by Takeda), HSP117 (developed by Hisamitsu), KRP103 (developed by Kyorin Pharm) and SLV317 (developed by Solvay). Chemical structures of the above-mentioned NK_1 antagonists are shown below and discussion of those compounds as well as other NK_1 antagonists is present in *Expert Opin. Ther. Patents* (2010) 20(8), pp1019-1045 by Huang et al.

The background of U.S. Patent No. 6,297,375 suggests that NK_1 antagonists are useful for treating a variety of conditions in which substance P (the natural ligand for the NK_1 receptor) is active. These conditions include depression, pain (especially pain resulting from inflammatory conditions such as migraine, rheumatoid arthritis, asthma, and inflammatory bowel disease), central nervous system (CNS) disorders such as Parkinson's disease and Alzheimer's disease, headache, anxiety, multiple sclerosis, attenuation of morphine withdrawal, cardiovascular changes, oedema, chronic inflammatory diseases such as rheumatoid arthritis, asthma/bronchial hyperreactivity and other respiratory diseases including allergic rhinitis, inflammatory diseases of the gut including ulcerative colitis and Crohn's disease, ocular injury and ocular inflammatory diseases. The background even mentions motion sickness and vomiting, but fails to call out nausea specifically.

Accordingly, there is a need in the art for more effective treatments of nausea and vomiting, particularly nausea and vomiting emanating from chemotherapy, radiotherapy and surgery. In addition, given the prolonged incidence of nausea and vomiting induced by these emetic events, there is a need for treating such nausea and vomiting for a prolonged period of time. Further, there is a need for the development of dosage forms to reduce drug-drug

interaction, improve stability, and potentiate effects of each component of the combined dosage forms.

OBJECTS OF THE INVENTION

Accordingly, it is an object of the invention to provide new methods for treating or preventing nausea and vomiting using an NK_1 antagonist, particularly netupitant.

It is another object of the invention to provide methods for treating or preventing nausea and vomiting in patients undergoing chemotherapy, radiotherapy, or surgery.

Still another object of the invention is to augment existing treatments for CINV, RINV or PONV by steroids and 5-HT_3 antagonists, and thereby provide additional protection against both nausea and vomiting, especially during the acute and delayed phases.

Another object of the invention is to provide a single combined dose of netupitant and a 5-HT_3 antagonist and to the use of that single dose without further dosing, for the treatment of nausea and vomiting during the acute and delayed phases of CINV, RINV or PONV.

It is another object to provide novel methods to treat nausea, vomiting, and other undesirable effects from moderately emetogenic and highly emetogenic chemotherapy ("MEC and HEC"), especially HEC, during the acute and delayed phases following such treatments.

It is another object to provide novel dosage forms to reduce drug-drug interaction, improve stability, enhance bioavailability and potentiate therapeutic effect of each component of the combined dosage forms comprising netupitant and/or 5-HT_3 antagonist and/or dexamethasone, in treating or preventing nausea and vomiting.

SUMMARY OF THE INVENTION

After extensive testing into the clinical effects of netupitant, it has unexpectedly been discovered that netupitant is active against nausea, and that a single dose of netupitant is able to treat nausea and vomiting in response to highly and moderately emetogenic chemotherapy for five consecutive days. It has also been discovered, quite unexpectedly, that netupitant exhibits unique binding habits to NK_1 receptors in the brain. In particular, it has been discovered that netupitant binds to NK_1 receptors in the striatum in a long-lasting manner, and that less than 20 or 30% of netupitant is released from striatum NK_1 receptors even ninety-six hours after administration. This is in stark contrast to aprepitant, in which receptor binding drops swiftly

over time, and must be dosed repeatedly if emesis control is desired throughout the delayed phase; and which shows no meaningful effect against nausea.

These discoveries have led to the development of a unique dosing regimen to treat nausea during the first day after an emesis-inducing event, in addition to the second, third, fourth and fifth days after such induction. Therefore, in one embodiment the invention provides a method of treating nausea and vomiting for a period of five consecutive days in a patient in need thereof, comprising administering to said patient netupitant or a pharmaceutically acceptable salt thereof in an amount which is therapeutically effective against nausea and vomiting during the acute and delayed phases, and which is effective to enter the systemic circulation, cross the blood brain barrier and occupy at least 70% of NK_1 receptors in the striatum seventy-two hours after said administration.

In another embodiment, the netupitant is combined with other anti-emetic agents, including a 5-HT_3 antagonist such as palonosetron and a corticosteroid such as dexamethasone, in a manner that results in even greater efficacy against nausea. It has been discovered that palonosetron is much more effective in combinations with netupitant than it is in combination with aprepitant, as reported by Grunberg et al., Support Cancer Care (2009) 17:589-594. In addition, palonosetron shows an improved pharmacokinetic profile (e.g., better bioavailability) when palonosetron is in combination with netupitant as opposed to palonosetron in single dose administration. Based on these discoveries, solid oral dosage forms have been developed that combine netupitant or another NK1 antagonist and palonosetron for the treatment of acute and delayed emesis.

It has also been discovered that netupitant potentiates the effect of dexamethasone, such that the dexamethasone is effective even when administered at sub-therapeutic doses (i.e. doses at which the dexamethasone would be ineffective if administered by itself). Therefore, in another embodiment the invention provides a combination therapy for treating nausea and vomiting for five consecutive days in a patient in need thereof, consisting essentially of:

- ~~Day 1 netupitant -- administering to said patient on day one netupinant or a pharmaceutically acceptable salt thereof, in an amount which is therapeutically effective against nausea and vomiting during the acute and delayed phases, and which is effective to enter the systemic circulation, cross the blood brain barrier and occupy at least 70% of NK_1 receptors in the striatum seventy-two hours after said administration;~~

Day 1 netupitant -- administering to said patient on day one netupinant or a pharmaceutically acceptable salt thereof, in an amount which is therapeutically effective against nausea and vomiting during the acute and delayed phases, and which is effective to enter the systemic circulation, cross the blood brain barrier and occupy at least 70% of NK_1 receptors in the striatum seventy-two hours after said administration;

- ~~Day 1 palonosetron -- administering to said patient on day one a therapeutically effective amount of a 5-HT_3 antagonist (preferably palonosetron) effective to treat said nausea and vomiting during the acute and delayed phases;~~
  Day 1 palonosetron -- administering to said patient on day one a therapeutically effective amount of a 5-HT_3 antagonist (preferably palonosetron) effective to treat said nausea and vomiting during the acute and delayed phases;
- ~~Day 1 dexamethasone -- administering to said patient on day one a first dose of dexamethasone which is ineffective against nausea and vomiting when administered alone, but effective against nausea and vomiting when administered in combination with said netupitant and palonosetron, wherein said first dose comprises from 50 to 70% of a minimum effective dose when administered alone; and~~

  Day 1 dexamethasone -- administering to said patient on day one a first dose of dexamethasone which is ineffective against nausea and vomiting when administered alone, but effective against nausea and vomiting when administered in combination with said netupitant and palonosetron, wherein said first dose comprises from 50 to 70% of a minimum effective dose when administered alone; and

- ~~Days 2-5 dexamethasone -- when the patient is undergoing highly emetogenic chemotherapy, administering to said patient, on days two, three and four, a second dose of dexamethasone which is ineffective against nausea and vomiting when administered alone, but effective against nausea and vomiting when administered in combination with said netupitant, wherein said second dose comprises from 40 to 60% of a minimum effective dose when administered alone on days two, three and four.~~

Days 2-5 dexamethasone — when the patient is undergoing highly emetogenic chemotherapy, administering to said patient, on days two, three and four, a second dose of dexamethasone which is ineffective against nausea and vomiting when administered alone, but effective against nausea and vomiting when administered in combination with said netupitant, wherein said second dose comprises from 40 to 60% of a minimum effective dose when administered alone on days two, three and four.

The dosage forms are extremely versatile and stable owing to their unique design and formulation. This versatility and stability is accomplished by formulating the NK1 antagonist and palonosetron in separate dosage forms and combining the dosage forms in one capsule. Thus, for example, the palonosetron can be formulated in a small gel-cap at a dose of around 0.5 mg, and the netupitant or other NK1 antagonist formulated in a tablet at a dose of about 100 to 150 mg. A capsule can then be filled with one or more palonosetron gel-caps and one or more netupitant (or other NK1 antagonist) tablets, depending on the therapeutic objective for the product. Because the palonosetron and NK1 antagonist are in separate dosage units, they can be formulated without regard to the stability of the other, and without degradation to by-products, for instance (3S)-3-[(3aS)-1-oxo- 2,3,3a,4,5,6-hexahydro-1*H*-benzo[*de*] isoquinoline-2-y1]-1-azoniabicyclo[2.2.2]octan-1-olate, a degradation by-product of palonosetron. As a result, the presently discovered dosage forms offer advantages, such as, reducing drug-drug interaction, improving stability, and potentiating effects of each component of the dosage forms in treating or preventing emesis.

Thus, in one embodiment the invention provides an orally administered dosage form comprising a combination of palonosetron and an NK1 antagonist (preferably netupitant), or a pharmaceutically acceptable salt or prodrug thereof.

In another embodiment the invention provides an orally administered capsule dosage form comprising (a) an outer shell; (b) one or more tablets housed within said outer shell, each comprising an NK1 antagonist (preferably netupitant) or a pharmaceutically acceptable salt or prodrug thereof and one or more pharmaceutically acceptable excipients; and (c) one or more soft-gel capsules housed within the outer shell, each comprising palonosetron or a pharmaceutically acceptable ester or prodrug thereof and one or more pharmaceutically acceptable excipients; wherein said dosage form comprises (3S)-3-[(3aS)-1-oxo- 2,3,3a,4,5,6-

hexahydro-1*H*-benzo [*de*] isoquinoline-2-y1]-1-azoniabicyclo[2.2.2]octan-l-olate in an amount that does not exceed 3 wt.%.

In still other embodiments the invention provides methods of treating acute and delayed-onset emesis by administering the dosage forms of the present invention to a human in need thereof, preferably shortly before the emesis inducing event.

Additional embodiments and advantages of the invention will be set forth in part in the description which follows, and in part will be obvious from the description, or may be learned by practice of the invention. The embodiments and advantages of the invention will be realized and attained by means of the elements and combinations particularly pointed out in the appended claims. It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as claimed.

BRIEF DESCRIPTION OF THE DRAWINGS

The accompanying drawings, which are incorporated in and constitute a part of this specification, illustrate several embodiments of the invention and together with the description, serve to explain the principles of the invention.

FIG. 1 depicts a capsule containing one soft-gel capsule of palonosetron and three tablets of netupitant.

FIG. 2 is a two dimensional graph plotting the pharmacokinetic profile of netupitant in humans following oral administration of netupitant alone and netupitant together with palonosetron.

FIG. 3 is a two dimensional graph plotting the pharmacokinetic profile of palonosetron in humans following oral administration of palonosetron alone and palonosetron together with netupitant.

FIG. 4 is a two dimensional graph plotting mean plasma concentrations of dexamethasone over time following administration with and without netupitant.

FIG. 5 contains two bar graphs that depict the average NK_1 receptor occupancy at 6, 24, 48, 72 and 96 hours after a single oral dose of 100, 300 and 450 mg. netupitant (N=2 for each dose) in striatum and occipital cortex, as measured using positron emission topography.

DETAILED DESCRIPTION OF THE INVENTION

The present invention may be understood more readily by reference to the following definitions and detailed description of preferred embodiments of the invention and the non-limiting Examples included therein.

Definitions and Use of Terms

When the singular forms "a," "an" and "the" or like terms are used herein, they will be understood to include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a pharmaceutical carrier" includes mixtures of two or more such carriers, and the like. The word "or" or like terms as used herein means any one member of a particular list and also includes any combination of members of that list.

When used herein the term "about" or "ca." will compensate for variability allowed for in the pharmaceutical industry and inherent in pharmaceutical products, such as differences in product strength and bioavailability due to manufacturing variations and time-induced product degradation. The term allows for any variation which in the practice of pharmaceuticals would allow the product being evaluated to be considered pharmaceutically equivalent or bioequivalent, or both if the context requires, to the recited strength of a claimed product.

Throughout the description and claims of this specification, the word "comprise" and variations of the word, such as "comprising" and "comprises," means "including but not limited to," and is not intended to exclude, for example, other additives, components, integers or steps.

As used herein, the term "Pharmaceutically acceptable" means that which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes that which is acceptable for veterinary use as well as human pharmaceutical use. In addition, the term "pharmaceutically acceptable salt" refers to a salt of a compound to be administered prepared from pharmaceutically acceptable non-toxic acids. Examples of suitable inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, sulfuric, and phosphoric. Suitable organic acids may be selected from aliphatic, aromatic, carboxylic and sulfonic classes of organic acids, examples of which are formic, acetic, propionic, succinic, camphorsulfonic, citric, fumaric, gluconic, isethionic, lactic, malic, mucic, tartaric, para-toluenesulfonic, glycolic, glucuronic, maleic, furoic, glutamic, benzoic, anthranilic, salicylic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, pantothenic, benzenesulfonic (besylate), stearic, sulfanilic, alginic, galacturonic, and the like.

Pharmaceutically acceptable salts of palonosetron include palonosetron hydrochloride. Pharmaceutically acceptable pro-drugs of netupitant include those described in U.S. Patent Nos. 6,593,472, 6,747,026 and 6,806,370, including the N-oxide of netupitant. The contents of these publications are incorporated herein by reference. When a molecule is referred to herein in its base or salt form, it will be understand also to encompass other pharmaceutically acceptable salt forms of the molecule.

As used herein, "therapeutically effective amount" refers to an amount sufficient to elicit the desired biological response. The therapeutically effective amount or dose will depend on the age, sex and weight of the patient, and the current medical condition of the patient. The skilled artisan will be able to determine appropriate dosages depending on these and other factors in addition to the present disclosure.

The minimum effective dose of dexamethasone, when used to treat CINV induced by highly emetogenic chemotherapy, has been demonstrated to be 20 mg. administered orally or by injection on day one, and sixteen mg. administered orally or by injection on days two, three and four. Jordan *et al.,* THE ONCOLOGIST, Vol. 12, No. 9, 1143-1150, September 2007. When used to treat CINV induced by moderately emetogenic chemotherapy, the minimum effective dose of dexamethasone is 20 mg. administered orally or by injection on day one, and zero mg. on days two, three and four.

The terms "treating" and "treatment," when used herein, refer to the medical management of a patient with the intent to cure, ameliorate, stabilize, or prevent a disease, pathological condition, or disorder. This term includes active treatment, that is, treatment directed specifically toward the improvement of a disease, pathological condition, or disorder, and also includes causal treatment, that is, treatment directed toward removal of the cause of the associated disease, pathological condition, or disorder. In addition, this term includes palliative treatment, that is, treatment designed for the relief of symptoms rather than the curing of the disease, pathological condition, or disorder; preventative treatment, that is, treatment directed to minimizing or partially or completely inhibiting the development of the associated disease, pathological condition, or disorder; and supportive treatment, that is, treatment employed to supplement another specific therapy directed toward the improvement of the associated disease, pathological condition, or disorder.

As used herein, the term "significantly" refers to a level of statistical significance. The level of statistical significant can be, for example, of at least $p<0.05$, of at least $p<0.01$, of at

least $p<0.005$, or of at least $p<0.001$. Unless otherwise specified, the level of statistical significance is $p<0.05$. When a measurable result or effect is expressed or identified herein, it will be understood that the result or effect is evaluated based upon its statistical significance relative to a baseline. In like manner, when a treatment is described herein, it will be understood that the treatment shows efficacy to a degree of statistical significance.

5-HT_3 antagonists include the various setrons such as, for example, palonosetron, ondansetron, dolasetron, tropisetron, and granisetron, and their pharmaceutically acceptable salts. A preferred 5-HT_3 antagonist is palonosetron, especially its hydrochloride salt.

"Highly emetogenic chemotherapy" refers to chemotherapy having a high degree of emetogenic potential, and includes chemotherapy based on carmustine, cisplatin, cyclophosphamide > 1500 mg/m^2, dacarbazine, dactinomycin, mechlorethamine, and streptozotocin.

"Moderately emetogenic chemotherapy" refers to chemotherapy having a moderate degree of emetogenic potential, and includes chemotherapy based on carboplatin, cyclophosphamide < 1500 mg/m^2, cytarabine > 1 mg/m^2, daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, and oxaliplatin.

Acute emesis refers to the first twenty-four hour period following an emesis-inducing event. Delayed emesis refers to the second, third, fourth and fifth twenty-four hour periods following an emesis-inducing event. When a treatment is said to be effective during the delayed phase, it will be understood to mean that the effectiveness of the treatment is statistically significant during the entire delayed phase, regardless of whether the treatment is effective during any particular twenty-four hour period of the delayed phase. It will also be understood that the method can be defined based upon its effectiveness during any one of the twenty-four hour periods of the delayed phase. Thus, unless otherwise specified, any of the methods of treating nausea and/or vomiting during the delayed phases, as described herein, could also be practiced to treat nausea and/or vomiting during the second, third, fourth or fifth twenty-four hour periods following an emesis inducing event, or an combination thereof.

When ranges are given by specifying the lower end of a range separately from the upper end of the range, it will be understood that the range can be defined by selectively combining any one of the lower end variables with any one of the upper end variables that is mathematically possible.

Methods of Treatment

As noted above, the invention is premised on several unique discoveries, and provides the following independent methods that can be practiced according to the present invention, including:

In a first principal embodiment, the invention provides a method of treating nausea and vomiting for a period of five consecutive days in a patient in need thereof, comprising administering to said patient netupitant or a pharmaceutically acceptable salt thereof in an amount which is therapeutically effective to treat nausea and vomiting during the acute and delayed phases, which enters the systemic circulation, crosses the blood brain barrier and occupies at least 70% of NK_1 receptors in the striatum seventy-two hours after said administration.

In a second principal embodiment, the invention provides a combination therapy for treating nausea and vomiting for five consecutive days in a patient in need thereof, comprising:

(i) ~~administering to said patient on day one netupitant or a pharmaceutically acceptable salt thereof, in an amount which is therapeutically effective to treat nausea and vomiting during the acute and delayed phases, which enters the systemic circulation, crosses the blood brain barrier and occupies at least 70% of NK_1 receptors in the striatum seventy-two hours after said administration;~~

administering to said patient on day one netupitant or a pharmaceutically acceptable salt thereof, in an amount which is therapeutically effective to treat nausea and vomiting during the acute and delayed phases, which enters the systemic circulation, crosses the blood brain barrier and occupies at least 70% of NK_1 receptors in the striatum seventy-two hours after said administration;

(ii) ~~administering to said patient on day one a therapeutically effective amount of a 5-HT_3 antagonist (preferably palonosetron, more preferably 0.5 mg. of oral palonosetron as palonosetron hydrochloride) effective to treat said nausea and vomiting during the acute and delayed phases;~~

administering to said patient on day one a therapeutically effective amount of a 5-HT_3 antagonist (preferably palonosetron, more preferably 0.5 mg. of oral palonosetron as palonosetron hydrochloride) effective to treat said nausea and vomiting during the acute and delayed phases;

(iii) ~~administering to said patient on day one a first dose of dexamethasone which is ineffective against nausea and vomiting when administered alone, but effective against nausea and vomiting when administered in combination with said netupitant and palonosetron, wherein said first dose comprises from 50 to 70% of a minimum effective dose when administered alone; and~~

administering to said patient on day one a first dose of dexamethasone which is ineffective against nausea and vomiting when administered alone, but effective against nausea and vomiting when administered in combination with said netupitant and palonosetron, wherein said first dose comprises from 50 to 70% of a minimum effective dose when administered alone; and

(iv) ~~if the patient is undergoing highly emetogenic chemotherapy, administering to said patient, on days two, three and four, a second dose of dexamethasone which is ineffective against nausea and vomiting when administered alone, but effective against nausea and vomiting when administered in combination with said netupitant, wherein said second dose comprises from 40 to 60% of a minimum effective dose when administered alone on days two, three and four.~~

if the patient is undergoing highly emetogenic chemotherapy, administering to said patient, on days two, three and four, a second dose of dexamethasone which is ineffective against nausea and vomiting when administered alone, but effective against nausea and vomiting when administered in combination with said netupitant, wherein said second dose comprises from 40 to 60% of a minimum effective dose when administered alone on days two, three and four.

Various sub-embodiments are envisaged for these principal embodiments. For example, the netupitant can be administered as a free base or a pharmaceutically acceptable salt thereof, but is preferably administered as the free base. In addition, the netupitant is preferably administered in an amount ranging from about 50 to about 500 mg., from about 200 to about 400 mg., and preferably about 300 mg., based on the weight of the free base. A preferred route

of administration for the netupitant is oral. In terms of binding to NK_1 receptors, the netupitant preferably binds to at least 80 or even 85% of NK_1 receptors in the striatum seventy-two hours after administration. As of ninety six hours after administration, the netupitant preferably binds less than 70, 60, 50 or even 40% of said NK_1 receptors.

The methods of the present invention are all effective at treating or preventing nausea and vomiting induced by numerous events, including chemotherapy induced nausea and vomiting ("CINV"), from moderately or highly emetogenic chemotherapy, radiation therapy induced nausea and vomiting ("RINV"), and post-operative nausea and vomiting ("PONV"). The method is preferably performed shortly before the emesis inducing event (i.e. no more than 1 or 2 hours before the event). The methods may be used to treat nausea and vomiting during the acute phase of emesis, or during the delayed phase.

The drugs specified by the individual embodiments may be administered by any suitable dosing regimen, as is well known in the art, but in a preferred embodiment the netupitant, 5-HT_3 antagonist and steroid are administered orally. A preferred oral dose of palonosetron ranges from about 0.075 to about 1.0 mg, or from about 0.25 to about 0.75 mg, but is preferably about 0.5 mg. A preferred oral dose of netupitant ranges from about 50 to 500 mg, or from about 200 to about 400 mg, but is preferably about 300 mg. A preferred dose of corticosteroid, preferably dexamethasone, is 12 mg administered orally or via injection on the first day of treatment, and 8 mg administered orally or via injection on the second, third and fourth days after said treatment.

It will be further understood that the netupitant can be administered in prodrug form, in which case the invention will provide a method of treatment by inducing plasma levels of netupitant, and in each case the plasma level of netupitant induced by the prodrug administration will correspond to the level attained by the administration of netupitant or its pharmaceutically acceptable salt, in the doses and routes of administration described herein.

Pharmaceutical Compositions

Various pharmaceutical compositions can be developed that make use of the combinations described herein. The composition can be administered by any appropriate route, for example, orally, parenterally, or intravenously, in liquid or solid form.

Preferred modes of administrations of the active compounds are injectable and/or oral. These compositions will generally include an inert diluent or an edible carrier. They may be enclosed in gelatin capsules (for oral use) or compressed into tablets (for oral or buccal use) or

formulated into troches (for buccal use). For these purposes, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition.

Tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a gliding such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring. When the dosage unit form is a capsule, it can contain, in addition to material of the above type, a liquid carrier such as a fatty oil. In addition, dosage unit forms can contain various other materials which modify the physical form of the dosage unit, for example, coatings of sugar, shellac, or other enteric agents.

The compounds can be administered as a component of an elixir, suspension, syrup, wafer, orally disintegrating film, orally disintegrating tablet, chewing gum or the like. A syrup may contain, in addition to the active compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors.

Solutions or suspensions used for injection can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride, mannitol and dextrose. An injectable preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

Combined Oral Dosage Forms

As discussed above, the invention provides versatile combined oral dosage forms of palonosetron and an NK1 antagonist that can be readily modified depending on the therapeutic objective, and that do not present issues of stability and degradation. In a preferred embodiment, the invention provides a capsule for oral administration made from a hard outer shell that houses one or more NK1 antagonist tablets and one or more palonosetron soft-gel

capsules. The finished capsule and the tablet(s) and soft-gel capsule(s) housed within the capsule shell are all preferably formulated as immediate release dosage forms. Netupitant and casopitant, and their pharmaceutically acceptable salts, are particularly preferred NK_1 antagonists for the combined oral dosage forms of this invention.

While the NK1 antagonist is preferably formulated in a solid tablet, it will be understood that it can be formulated in any solid form that is suitable for oral administration including, for example, a tablet or capsule (hard or soft-gel). In a preferred embodiment, the NK1 antagonist is formulated in a tablet. The number of NK1 antagonist units contained within the combined dosage form can be, for example, from 1 to 10, 1 to 5, or 1 to 3. The netupitant units within the combined dosage form can provide anywhere from 50 to 500 mg of netupitant on an aggregate basis, preferably from 100 to 350 mg. Each netupitant unit preferably comprises from 50 to 200 mg of netupitant, more preferably 100 to 150 mg of netupitant, and most preferably 100 or 150 mg of netupitant.

The palonosetron can also be formulated in any solid form that is suitable for oral administration, although it is preferably formulated as a soft-gel capsule. Non-limiting examples of suitable palonosetron soft-gel capsules are provided in PCT publication WO 2008/049552, the contents of which are hereby incorporated by reference. The number of palonosetron units within the combined dosage from can be, for example, from 1 to 5, from 1 to 3 or just 1. Each of the palonosetron units within the combined dosage form can provide anywhere from 0.01 to 5.0 mg palonosetron, preferably from 0.1 to 1.0 mg palonosetron on an aggregate basis. Each palonosetron unit will preferably comprise from 0.1 to 1.0 mg of palonosetron, most preferably about 0.25, 0.5, 0.75 or 1.0 mg of palonosetron.

Figure 1 illustrates an exemplary embodiment of a combined oral dosage form of palonosetron and netupitant. The dosage form 10 comprises a two piece hard outer shell that includes a body 20 and a cap 22. The dosage form 10 contains one palonosetron soft-gel capsule 30 (preferably containing 0.5 mg of palonosetron) and three netupitant tablets 40 (each preferably containing 100 mg of netupitant).

Hard Outer Shell

The hard outer shell of the present invention can be made of any pharmaceutically acceptable material that dissolves in gastric fluids. Preferred materials for the hard outer shell include, for example, gelatin, cellulose, starch, or hydroxypropyl methylcellulose (HPMC). In a

particular embodiment of the invention, the hard outer shell has a maximum oxygen permeability. Preferably, the oxygen permeability is less about 1.0×10^{-3}, 5.0×10^{-4}, 1.0×10^{-4}, 5.0×10^{-5}, or even 2.0×10^{-5} ml·cm/(cm^2·24 hr. atm).

The hard outer shell can be a continuous structure. Alternatively, the hard outer shell can be a two-piece hard capsule.

Soft-Gel Capsule

The soft-gel capsule used for the palonosetron preferably comprises a soft outer shell and a liquid inner fill composition comprising palonosetron hydrochloride. Non-limiting examples of suitable palonosetron soft-gel capsules are provided in PCT publication WO 2008/049552, the contents of which are hereby incorporated by reference.

The soft outer shell of the soft-gel capsule can contain any type of material that dissolves in gastric fluids. Preferred materials for the soft outer shell include, for example, gelatin, cellulose, starch, or hydroxypropyl methylcellulose (HPMC). The soft-gel capsule can further comprise shell excipients such as glycerin, sorbitol, and colorants/opacifers such as titanium dioxide. The soft-gel capsule can further include solvents such as purified water. In particular embodiments of the invention, the outer shell has a maximum oxygen permeability, preferably of no more than 1.0×10^{-3}, 5.0×10^{-4}, 1.0×10^{-4}, 5.0×10^{-5}, or even 2.0×10^{-5} ml·cm/(cm^2·24 hr. atm). Suitable soft-gel capsules include the 1.5-oval gelatine capsule shell manufactured by Catalent Pharma Solutions.

The liquid fill is preferably composed predominantly of one or more lipophilic components in an amount of from 50 wt.% to 99 wt.%, preferably from 75 wt.% to 98 wt.%. Preferred lipophilic components include, for example, mono- and di-glycerides of fatty acids, especially including the mono- and di-glycerides of capryl/capric acid. The liquid fill may also contain glycerin, preferably in an amount of from 1 to 15 wt.%, more preferably from 2 to 10 wt.%. In one preferred embodiment, both the shell and the inner fill composition comprise glycerin. In another preferred embodiment, the liquid fill comprises about 0.25, 0.50, 0.75 mg., or more of palonosetron as palonosetron hydrochloride.

The fill composition may comprise various means to facilitate the transition of palonosetron from the dosage form to the gastrointestinal fluids of the GI tract, so that the palonosetron may be more readily absorbed into the bloodstream. For example, the liquid fill composition may contain a surfactant, optimally in an amount of from 0.1 wt.% to 6 wt.%,

from 0.5 wt.% to 5 wt.%, or from 1.0 wt.% to 3.0 wt.%. The liquid fill composition preferably comprises greater than 0.1, 0.5, or 1.0 wt.% of surfactant, and less than 10, 8, 5, 4, or even 4 wt.% of surfactant. A particularly preferred surfactant is polyglyceryl oleate.

Alternatively or in addition, the transitioning means for a liquid filled capsule may comprise water that forms a single phase or microemulsion with the other liquid ingredients in the excipient base. The liquid fill composition preferably comprises from 0.05 wt.% to 30 wt.% water, from 1 wt.% to 20 wt.% water, or from 2 wt.% to10 wt.% water. The liquid fill preferably comprises greater than 0.1, 0.5 or 1.0 wt.% water, and less than 20, 15, 10, 8 or 5 wt.% water.

The active agent, which is preferably palonosetron hydrochloride, is preferably present in the fill composition in an amount ranging from 0.01 to 10.0 wt.%, from 0.05 to 5.0 wt.%, or from 0.1 wt.% to 2.0 wt.%. Alternatively, particularly stable formulations have been found where the concentration of palonosetron exceeds 0.3%, preferably at a concentration no greater than 1 wt.%.

Tablet

The tablets of the present invention can include from 20 to 95 wt.% of NK1 antagonist (preferably netupitant), and preferably comprises from 60 to 80 wt.% of netupitant. In addition, the tablets can contain diluents, disintegrants, surfactants, binders, glidants, and/or lubricants. In a particular embodiment, the tablet comprises from 5 to 25 wt.% of microcrystalline cellulose. The microcrystalline cellulose can function as a diluent and disintegrant, and preferably comprises 15 wt.% of the tablet. Another suitable disintegrant is sodium croscaramellose, which can be present in the tablet in an amount of from 1 to 5 wt.%, preferably 2 wt.%.

A suitable binder for use in the tablet is polyvinylpyrrolidone, which can be present in the tablet in an amount from 1 to 10 wt.% of the tablet, and preferably 5 wt.%. A suitable glidant for use in the tablet is colloidal silicon dioxide, which can be present in the tablet in an amount of 2 wt.%. Suitable lubricants for use in the tablet include sodium stearyl fumarate and magnesium stearate, which can be present in the tablet in an amount of 0.7 wt.% and 0.35 wt.%, respectively.

Application of The Combined Oral Dosage Forms

The invention further provides a method of treating emesis comprising orally administering to a patient suffering from emesis, or at risk for suffering emesis, a dosage form

of the present invention. In still further embodiments, the invention provides methods of treating emesis by administering one or more of the dosage forms described herein. The dosage form is preferably administered shortly before the emesis inducing event (i.e. no more than 2 hours before the event). The emesis may be acute phase emesis (i.e. emesis experienced within about 24 hours of an emesis inducing event), or delayed emesis (i.e. emesis experienced after the acute phase, but within seven, six, five or four days of an emesis inducing event). The emesis may constitute chemotherapy induced nausea and vomiting ("CINV"), from moderately or highly emetogenic chemotherapy, radiation therapy induced nausea and vomiting ("RINV"), or postoperative nausea and vomiting ("PONV").

EXAMPLES

The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how the compounds claimed herein are made and evaluated, and are intended to be purely exemplary of the invention and are not intended to limit the scope of what the inventors regard as their invention. Efforts have been made to ensure accuracy with respect to numbers (e.g., amounts, temperature, etc.) but some errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, temperature is in °C or is at room temperature, and pressure is at or near atmospheric.

EXAMPLE 1 — PREPARATION OF ORAL DOSAGE FORM

In a preferred embodiment the combination is administered in a capsule oral dosage form, wherein the capsule houses one or more soft-gel capsules for the palonosetron and one or more hard tablets for the netupitant. Table 1 below describes a representative formulation for a soft-gel capsule containing 0.5 mg of palonosetron, suitable for inclusion in such a hard outer shell.

TABLE 1: REPRESENTATIVE SOFT-GEL FORMULATION

Ingredient	Approximate Amount	Function
Fill Solution		
Palonosetron HC1	0.56[1]	Active
Mono- and di-glycerides of Capryl/Capric Acid (Capmul MCM)	62.19	Solvent vehicle
Glycerin, anhydrous, USP/Ph Eur	3.37	Plasticizer
Polyglyceryl oleate (Plurol Oleique CC 497)	0.87	Surfactant
Purified water, USP/Ph Eur	2.94	Co-solvent
Butylated hydroxyanisole (BHA), NF/Ph Eur	0.07	Antioxidant
Nitrogen	-	
Theoretical fill weight	70.00 mg	
Gelatine Capsule Shell, 1.5-oval (Catalent Pharma Solutions)[2]		
Gelatine (type 195), NF/Ph Eur	-	Shell
Sorbitol Special/Glycerin Blend 50/50	-	Plasticizer
Titanium dioxide, USP/Ph Eur	-	Colorant/Opacifier
Purified water, USP/Ph Eur	-	Solvent

[1]Corresponds to 0.50 mg. free base

[2]Quantitative composition of capsule shell is proprietary to Catalent Pharma Solutions

Table 2 below describes a representative formulation for a tablet containing 100 mg. of netupitant, suitable for inclusion in a hard shell.

TABLE 2: REPRESENTATIVE TABLET FORMULATION

Ingredient	Approximate Amount (mg/Tablet)	Function
Netupitant, milled	100	Active
Microcrystalline cellulose pH 101	20.5	Diluent and disintegrant
Sucrose Lauric Acid Esters	10.0	Surfactant
Polyvinilpyrrolidone K30	7.0	Binder
Sodium croscaramellose	3.0	Disintegrant
Colloidal Silicon Dioxide	3.0	Glidant
Sodium Stearyl Fumarate	1.0	Lubricant
Magnesium Stearate	0.5	Lubricant
Total weight	145 mg	

EXAMPLE 2 — PHARMACOKINETICS OF COMBINED DOSAGE FORM

Objective

The effects of palonosetron on the pharmacokinetics (PK) of netupitant and the effects of netupitant on the PK of palonosetron were examined in healthy volunteers.

Methods

A randomized, open, 3-way crossover study was conducted. Each subject participated in 3 treatment periods, each lasting approximately 12 days (Day -1 to Day 11). The treatment periods were separated by wash-out periods of no less than 14 days (between Day 1 of any 2 consecutive treatment periods).

The following treatments were investigated:

Treatment A: oral netupitant 450 mg. administered as single dose of three 150 mg. capsules.

Treatment B: oral palonosetron 0.75 mg. and oral netupitant 450 mg. administered simultaneously as three capsules of 150 mg. netupitant followed by 1 capsule of 0.75 mg. palonosetron.

Treatment C: oral palonosetron 0.75 mg. administered as single dose as one 0.75 mg. capsule.

Doses were administered under fasting conditions. Subjects fasted over-night for approximately 10 hours. Water, however, was permitted up to 1 hour pre-dose. Food intake was permitted 4 hours post-dose, and water was allowed ad libitum 1 hour post-dose.

Doses were administered with the subject in an upright position. The subjects remained in an upright position for 4 hours post-dose. The capsules were swallowed whole with 250 mL of room-temperature tap water. Repeated PK blood sampling (for netupitant and/or palonosetron) was performed.

Results

The primary PK variables assessed for netupitant and palonosetron were the maximum plasma concentration observed (C_{max}), the area under the plasma concentration versus time curve from time zero to the last quantifiable sampling time point (t) (AUC_{0-t}), and the area under the plasma concentration versus time curve from time zero to infinity (AUC_{0-inf}). The secondary PK variables assessed were the terminal elimination half-life ($t_{½, z}$), and the time at which the maximum plasma concentration was observed (t_{max}). Results are depicted in below Tables 3 and 4, as well as Figures 2 and 3.

Table 3: Summary of Netupitant Pharmacokinetic Parameters

Parameter	Netupitant 450 mg	Palonosetron 0.75 mg + Netupitant 450 mg
AUC_{0-t} [h*µg/L]	22808 (7270)	22775 (10064)
AUC_{o-inf} [h*µg/L]	25927 (10156)	26241 (13219)
C_{max} [µg/L]	650.2 (257.8)	659.7 (325.7)
t_{max} (h)	4.50 (3.00 ; 24.00)	4.50 (3.00 ; 23.95)
$t_{½,z}$ (h)	71.81 (37.10 ; 261.61)	78.31 (50.17 ; 196.13)

Mean and SD are shown, except for t_{max} and $t_{½}$, where median and range are shown.

As can be seen in Table 4 below, palonosetron shows a better pharmacokinetic profile when combined with Netupitant as opposed to administered as a single dose of palonosetron, for example, the greater AUC, the larger $C_{max,}$ the shorter t_{max}, (the median t_{max} was 0.5 hour shorter after administration of palonosetron in combination with netupitant), and the longer $t_{½,z}$.

Table 4: Summary of Palonosetron Pharmacokinetic Parameters

Parameter	Palonosetron 0.75 mg	Palonosetron 0.75 mg + Netupitant 450 mg
AUC_{0-t} [h*µg/L]	67415 (19554)	74230 (24866)
AUC_{0-inf} [h*µg/L]	70813 (20415)	77254 (25402)
C_{max} [µg/L]	1638.4 (415.5)	1863.1 (487.1)
t_{max} (h)	5.02 (4.00 ; 8.00)	4.50 (3.00 ; 6.02)
$t_{½,z}$ (h)	34.73 (19.61 ; 70.46)	36.91 (20.23 ; 56.08)

Mean and SD are shown, except for t_{max} and $t_{½}$, where median and range are shown.

EXAMPLE 3: NETUPITANT + DEXAMETHASONE DRUG INTERACTION STUDY

The effect of netupitant on orally administered dexamethasone pharmacokinetics was evaluated in this study. This was a randomized, open, 3-period crossover study utilizing an incomplete Latin Square design where subjects were given dexamethasone alone, or oral Netupitant 100 mg., 300 mg. or 450 mg. each given with dexamethasone. Netupitant was given

orally on Day 1 only. The dexamethasone regimen for each treatment was 20 mg. orally Day 1, followed by 8 mg. orally every 12 hours from Day 2 through Day 4. Nineteen subjects (12 male and 7 female) completed the study (i.e., all 3 treatment periods).

Mean plasma concentrations of dexamethasone were higher when dexamethasone was co-administered with netupitant (Figure 4). The increase appeared to be dependant on the netupitant exposure.

The AUC_{0-24} (Day 1) of dexamethasone increased 1.5, 1.7 and 1.8-fold with co-administration of 100, 300 and 450 mg. netupitant, respectively. The AUC_{24-36} (Day 2) of dexamethasone increased 2.1, 2.4 and 2.6-fold and AUC_{84-108} and AUC_{84-inf} (Day 4) increased 1.7, 2.4 and 2.7-fold, with co-administration of 100, 300 and 450 mg. netupitant, respectively. Dexamethasone C_{max} on Day 1 was only slightly affected by co-administration of netupitant (1.1-fold increase during co-administration with 100 and 300 mg. netupitant, respectively, and 1.2-fold increase during co-administration with 450 mg. netupitant). C_{max} on Day 2 and Day 4 was increased approximately 1.7-fold in subjects administered netupitant. Dexamethasone C_{min} on Days 2-4 was increased approximately 2.8, 4.3 and 4.6-fold with co-administration of 100, 300 and 450 mg. netupitant, respectively. This clearly shows that the co-administration of netupitant and dexamethasone enhances the bioavailability of dexamethasone and provides a better therapeutic window of dexamethasone.

EXAMPLE 4: NETUPITANT PET RECEPTOR OCCUPANCY STUDY

This was a randomized, open-label, positron emission tomography (PET) study using 11C-GR205171 as tracer in 6 healthy male volunteers (2 per dose level) receiving single doses of netupitant (100, 300 or 450 mg) to investigate the degree of occupancy of NK_1 receptors in human brain, and to determine the relationship between plasma concentration of netupitant and NK_1 receptor occupancy (RO).

The anticipated high NK_1-RO (90% or higher) close to the expected C_{max} (6 hours post dose) was reached for striatum, occipital cortex, frontal cortex and anterior cingulate in 3 of 6 subjects of whom 1 received 300 mg. and 2 received 450 mg. of netupitant as a single oral dose.

All doses showed a relatively long duration of blockade of NK_1 receptors and the decline over time was dose dependent. In the 100 mg. dose group, 4 of 6 regions still had a mean NK_1-RO over 70% at 96 hours post dose. In the highest dose group (450 mg), 5 of 6

regions had a mean NK_1-RO of 80% or higher at 96 hours post dose. A comparison of the results for the dose groups (100 mg., 300 mg. and 450 mg) showed a consistent but small increase in NK_1-RO_s with increasing netupitant dose. (Figure 5)

EXAMPLE 5: CLINICAL EFFICACY STUDY

A phase 2 trial evaluated three single doses of netupitant combined with palonosetron and dexamethasone compared to palonosetron alone and dexamethasone to obtain dose ranging information for netupitant used with oral palonosetron in the CINV patient population.

The objective of the study was to compare the efficacy and safety of three single oral doses of netupitant combined with oral palonosetron and given with dexamethasone, versus oral palonosetron-alone given with dexamethasone (without netupitant) for the prevention of highly emetogenic chemotherapy (HEC)-induced nausea and vomiting. The FDA-approved oral aprepitant regimen given with IV ondansetron and dexamethasone was included in the study as an active comparator for exploratory purposes. The FDA-approved oral palonosetron 0.5 mg. dose was used in each applicable treatment group in this study.

This was a multicenter, randomized, double-blind, double-dummy, parallel group, stratified study. Eligible patients were randomized (stratified by gender) to one of the following treatment groups:

~~Group 1 — 0.5 mg. oral palonosetron on Day 1 (with an oral dexamethasone standard regimen: 20 mg. on Day 1 and 8 mg. BID from Day 2 through Day 4)~~

~~Group 2 — 100 mg. oral netupitant plus 0.5 mg. oral palonosetron on Day 1 (with an oral dexamethasone adjusted regimen*: 12 mg. on Day 1 and 8 mg. daily from Day 2 through Day 4)~~

~~Group 3 — 200 mg. oral netupitant plus 0.5 mg. oral palonosetron on Day 1 (with an oral dexamethasone adjusted regimen*: 12 mg. on Day 1 and 8 mg. daily from Day 2 to Day 4)~~

~~Group 4 — 300 mg. oral netupitant plus 0.5 mg. oral palonosetron on Day 1 (with dexamethasone adjusted regimen*: 12 mg. on Day 1 and 8 mg. daily from Day 2 to Day 4)~~

~~Group 5 — 125 mg. oral aprepitant plus IV ondansetron 32 mg. (both on Day 1) then 80 mg. oral aprepitant on Day 2 and Day 3, (all with an oral dexamethasone adjusted regimen: 12 mg. on Day 1 and 8 mg. daily from Day 2 through Day 4)~~

Group 1 — 0.5 mg. oral palonosetron on Day 1 (with an oral dexamethasone standard regimen: 20 mg. on Day 1 and 8 mg. BID from Day 2 through Day 4)

Group 2 — 100 mg. oral netupitant plus 0.5 mg. oral palonosetron on Day 1 (with an oral dexamethasone adjusted regimen*: 12 mg. on Day 1 and 8 mg. daily from Day 2 through Day 4)

Group 3 — 200 mg. oral netupitant plus 0.5 mg. oral palonosetron on Day 1 (with an oral dexamethasone adjusted regimen*: 12 mg. on Day 1 and 8 mg. daily from Day 2 to Day 4)

Group 4 — 300 mg. oral netupitant plus 0.5 mg. oral palonosetron on Day 1 (with dexamethasone adjusted regimen*: 12 mg. on Day 1 and 8 mg. daily from Day 2 to Day 4)

Group 5 — 125 mg. oral aprepitant plus IV ondansetron 32 mg. (both on Day 1) then 80 mg. oral aprepitant on Day 2 and Day 3, (all with an oral dexamethasone adjusted regimen: 12 mg. on Day 1 and 8 mg. daily from Day 2 through Day 4)

In addition, a Group 6 was added to the analysis for comparative purposes, based on the results reported by Grunberg et al., Support Cancer Care (2009) 17:589-594:

~~Group 6 — 285 mg. oral aprepitant plus 20 mg. oral dexamethasone plus 0.2 mg. palonosetron i.v. (all on Day 1) then 80 mg. oral aprepitant~~

Group 6 — 285 mg. oral aprepitant plus 20 mg. oral dexamethasone plus 0.2 mg. palonosetron i.v. (all on Day 1) then 80 mg. oral aprepitant

The primary efficacy endpoint was the complete response rate (defined as no emetic episodes, no rescue medication) within 120 hours after the start of the highly emetogenic chemotherapy administration. Secondary efficacy endpoints were:

- ~~Complete response for the 0-24 hour interval (acute phase); and for the 25-120 hour interval (delayed phase);~~
  Complete response for the 0-24 hour interval (acute phase); and for the 25-120 hour interval (delayed phase);
- ~~Complete protection (defined as no emesis, no rescue therapy, no significant nausea); Total control (defined as no emesis, no rescue therapy and no nausea); No nausea (maximum VAS <5 mm); No significant nausea (maximumVAS <25 mm); No rescue medication; No emesis. These endpoints were evaluated for the 0-120 hour interval (overall), acute and delayed phase.~~

Complete protection (defined as no emesis, no rescue therapy, no significant nausea); Total control (defined as no emesis, no rescue therapy and no nausea); No nausea (maximum VAS <5 mm); No significant nausea (maximumVAS <25 mm); No rescue medication; No emesis. These endpoints were evaluated for the 0-120 hour interval (overall), acute and delayed phase.

- ~~Time to first emetic episode, Time to first rescue medication, Time to treatment failure (based on time to the first emetic episode or time to the first rescue medication, whichever occurs first);~~

  Time to first emetic episode, Time to first rescue medication, Time to treatment failure (based on time to the first emetic episode or time to the first rescue medication, whichever occurs first);

- ~~Severity of nausea for the overall, acute and delayed phase; • Patient global satisfaction with anti-emetic therapy by means of VAS for each 24 hour interval.~~

  Severity of nausea for the overall, acute and delayed phase; • Patient global satisfaction with anti-emetic therapy by means of VAS for each 24 hour interval.

Complete response rates are summarized in Table 5. The percent of patients with complete response over 0-120 hours after start of cisplatin administration was 76.5% in the palonosetron alone group and 87.4%, 87.6%, and 89.6% in the netupitant 100 mg., 200 mg., and 300 mg. groups, respectively. Differences from palonosetron-alone were greater than 10% (10.9% to 13.2%). All doses of netupitant were statistically superior to palonosetron alone (p-value=0.004 for the netupitant 300 mg. combination group).

TABLE 5: COMPLETE RESPONSE RATE FOR THE OVERALL, ACUTE AND DELAYED PHASE: MFAS Population

Efficacy endpoint	Palo alone (n=136)	Palo + Netu 100 mg (n=135)	Palo + Netu 200 mg (n=137)	Palo + Netu 300 mg (n=135)	Aprepitant Regimen (N=134)
CR, Overall Phase, 0-120h					
Percent of Patients	76.5	87.4	87.6	89.6	86.6
Difference from Palo alone (%)		10.9	11.1	13.2	10.1
p-value (*)		0.018	0.017	0.004	0.027
CR, Acute Phase, -24h					
Percent of Patients	89.7	93.3	92.7	98.5	94.8
Difference from Palo alone (%)		3.6	3.0	8.8	5.1
p-value (*)		0.278	0.383	0.007	0.114
CR, Delayed Phase, 25-120h					
Percent of Patients	80.1	90.4	91.2	90.4	88.8
Difference from Palo alone (%)		10.2	11.1	10.2	8.7
p-value (*)		0.018	0.010	0.018	0.043

(*) p-value from logistic regression analysis, aprepitant p-value from post-hoc logistic regression analysis.

Table 6 summarizes results for main secondary endpoints. In the overall phase, 76.5% of patients in the palonosetron-alone group did not experience emesis, while 87.4, 87.6, and 91.1% of patients did not experience emesis in the netupitant 100 mg., 200 mg. and 300 mg. combination groups, respectively ($p<0.05$ for all doses).

TABLE 6: SUMMARY OF SECONDARY EFFICACY RESULTS: PERCENT OF PATIENTS, MFAS POPULATION

Efficacy endpoint	**Palo alone (n=136)**	**Palo + Netu 100 mg (n=135)**	**Palo + Netu 200 mg (n=137)**	**Palo + Netu 300 mg (n=135)**	**Aprepitant Regimen (N=134)**	**Palo+Aprep 285 mg (N=41)****
No Emesis						
Overall	76.5	87.4*	87.6*	91.1*	87.3	
Acute	89.7	93.3	92.7	98.5*	94.8	
Delayed	80.1	90.4*	91.2*	91.9*	89.6*	
No Rescue						
Overall	95.6	97.8	100	98.5	97.8	
Acute	97.8	99.3	100	100	100	
Delayed	97.1	97.8	100	98.5	97.8	
No Nausea						
Overall	50.7	54.8	62.0	61.5	58.2	32
Acute	75.0	72.6	77.4	80.0	77.6	59
Delayed	53.7	59.3	65.0	68.1*	60.4	41
No Significant Nausea						
Overall	79.4	80.0	86.1	89.6*	85.8	56
Acute	93.4	94.1	94.2	98.5*	94.0	79
Delayed	80.9	81.5	89.8*	90.4*	88.1	59
Total Control						
Overall	50.0	54.8	61.3	59.3	56.0	
Acute	71.3	71.9	76.6	80.0	74.6	
Delayed	52.2	59.3	65.0*	65.9*	58.2	
Complete						

Protection						
Overall	69.9	76.3	80.3*	83.0*	78.4	51
Acute	87.5	89.6	88.3	97.0*	89.6	76
Delayed	73.5	80.0	87.6*	84.4*	82.1	66

* p-value ,0.05 compared with palonosetron-alone; aprepitant comparisons p-values calculated by post-hoc analysis

** As reported by Grunberg et al., Support Cancer Care (2009) 17:589-594

EXAMPLE 7: COMPARATIVE RESULTS OF APREPITANT DOSING REGIMEN

The following Table 8 reports the results observed for an aprepitant dosing regimen, as described in the FDA approved prescribing information for aprepitant, which demonstrates, among other things, that aprepitant has no meaningful effect on nausea. Table 7 reports the dosing regimen:

TABLE 7

Treatment Regimen	Day 1	Day 2 to 4
Aprepitant	Aprepitant 125mg PO Dexamethasone 12 mg PO Ondansetron 32 mg I.V.	Aprepitant 80mg PO Daily (Days 2 and 3 only) Dexamethasone 8 mg PO Daily (morning)

TABLE 8

Percent of Patients Receiving Highly Emetogenic Chemotherapy Responding by Treatment

Group and Phase for Study 1 – Cycle 1

ENDPOINTS	Aprepitant Regimen (N=260)† %	Standard Therapy (N=261)† %	p-Value
PRIMARY ENDPOINT			
Complete Response			
Overall‡	73	52	<0.001
OTHER PRESPECIFIED ENDPOINTS			
Complete Response			
Acute phase[1]	89	78	<0.001
Delayed Phase[2]	75	56	<0.001
Complete Protection			
Overall	63	49	0.001
Acute phase	85	75	NS*
Delayed phase	66	52	<0.001
No Emesis			
Overall	78	55	<0.001
Acute phase	90	79	0.001
Delayed phase	81	59	<0.001
No Nausea			
Overall	48	44	NS**
Delayed phase	51	48	NS**
No Significant Nausea			
Overall	73	66	NS**
Delayed phase	75	69	NS**

† N: Number of patients (older than 18 years of age) who received cisplatin, study drug, and had at least one post-treatment efficacy evaluation.

‡ Overall: 0 to 120 hours post-cisplatin treatment.

[1] Acute phase: 0 to 24 hours post-cisplatin treatment.

[2] Delayed phase: 25 to 120 hours post-cisplatin treatment.

* Not statistically significant when adjusted for multiple comparisons.

****

Throughout this application, various publications are referenced. The disclosures of these publications in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art to which this invention pertains. It will be apparent to those skilled in the art that various modifications and variations can be made in the present invention without departing from the scope or spirit of the invention. Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims.

PTO/AIA/01 (06-12)
Approved for use through 01/31/2014. 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 displays a valid OMB control number.

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

Title of Invention	Compositions and Methods For Treating Centrally Mediated Nausea And Vomitting

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 14/069,970 filed on 11/01/2013.

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: Fabio Trento Date (Optional): December 12, 2014

Signature: [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.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

PTO/AIA/01 (06-12)
Approved for use through 01/31/2014. 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 displays a valid OMB control number.

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

Title of Invention	Compositions and Methods For Treating Centrally Mediated Nausea And Vomitting

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 14/069,970 filed on 11/01/2013.

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: Sergio Cantoreggi Date (Optional): December 12, 2014

Signature: /SC/

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.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

PTO/AIA/01 (06-12)
Approved for use through 01/31/2014. 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 displays a valid OMB control number.

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

Title of Invention	Compositions and Methods For Treating Centrally Mediated Nausea And Vomitting

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 14/069,970 filed on 11/01/2013.

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: Giorgia Rossi Date (Optional): December 12, 2014

Signature: Giorgia Rossi

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.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

PTO/AIA/01 (06-12)
Approved for use through 01/31/2014. 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 displays a valid OMB control number.

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

Title of Invention	Compositions and Methods For Treating Centrally Mediated Nausea And Vomitting

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 14/069,970 filed on 11/01/2013.

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: Roberta Cannella Date (Optional): December 17, 2014

Signature: Roberta Cannella

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.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

PTO/AIA/01 (06-12)
Approved for use through 01/31/2014. 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 displays a valid OMB control number.

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

Title of Invention	Compositions and Methods For Treating Centrally Mediated Nausea And Vomitting

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 14/069,970 filed on 11/01/2013.

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: Daniele Bonadeo Date (Optional): December 17, 2014

Signature: Daniele Bonadeo

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.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Doc Code: PA..
Document Description: Power of Attorney

PTO/AIA/82A (07-13)
Approved for use through 11/30/2014. OMB 0651-0051
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 displays a valid OMB control number.

TRANSMITTAL FOR POWER OF ATTORNEY TO ONE OR MORE REGISTERED PRACTITIONERS

NOTE: This form is to be submitted with the Power of Attorney by Applicant form (PTO/AIA/82B) to identify the application to which the Power of Attorney is directed, in accordance with 37 CFR 1.5, unless the application number and filing date are identified in the Power of Attorney by Applicant form. If neither form PTO/AIA/82A nor form PTO/AIA82B identifies the application to which the Power of Attorney is directed, the Power of Attorney will not be recognized in the application.

Application Number	Not Yet Known
Filing Date	Herewith
First Named Inventor	Fabio TRENTO
Title	COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING
Art Unit	Not Yet Known
Examiner Name	Not Yet Known
Attorney Docket Number	244168.000015US6

SIGNATURE of Applicant or Patent Practitioner

Signature	/Clark G. Sullivan/	Date (Optional)	January 21, 2016
Name	Clark G. Sullivan	Registration Number	36,942
Title (if Applicant is a juristic entity)	Attorney for applicant		
Applicant Name (if Applicant is a juristic entity)	Helsinn Healthcare SA		

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. If more than one applicant, use multiple forms.

☑ *Total of 1 forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. 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 3 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.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Doc Code: PA..
Document Description: Power of Attorney

PTO/AIA/82B (07-13)
Approved for use through 11/30/2014. OMB 0651-0031
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 displays a valid OMB control number

POWER OF ATTORNEY BY APPLICANT

I hereby revoke all previous powers of attorney given in the application identified in either the attached transmittal letter or the boxes below.

Application Number	Filing Date

(Note: The boxes above may be left blank if information is provided on form PTO/AIA/82A.)

☑ I hereby appoint the Patent Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above: 06980

OR

☐ I hereby appoint Practitioner(s) named in the attached list (form PTO/AIA/82C) as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the patent application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above. (Note: Complete form PTO/AIA/82C.)

Please recognize or change the correspondence address for the application identified in the attached transmittal letter or the boxes above to:

☑ The address associated with the above-mentioned Customer Number

OR

☐ The address associated with Customer Number:

OR

Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Email			

I am the Applicant (if the Applicant is a juristic entity, list the Applicant name in the box):

HELSINN HEALTHCARE SA

☐ Inventor or Joint Inventor (title not required below)

☐ Legal Representative of a Deceased or Legally Incapacitated Inventor (title not required below)

☑ Assignee or Person to Whom the Inventor is Under an Obligation to Assign (provide signer's title if applicant is a juristic entity)

☐ Person Who Otherwise Shows Sufficient Proprietary Interest (e.g., a petition under 37 CFR 1.46(b)(2) was granted in the application or is concurrently being filed with this document) (provide signer's title if applicant is a juristic entity)

SIGNATURE of Applicant for Patent

The undersigned (whose title is supplied below) is authorized to act on behalf of the applicant (e.g., where the applicant is a juristic entity).

Signature		Date (Optional)	MAY 28, 2015
Name	MATTEO TISCAGLIA		
Title	SENIOR DIRECTOR, LEGAL AFFAIRS		

NOTE: Signature - This form must be signed by the applicant in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. If more than one applicant, use multiple forms.

☐ Total of forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. 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 3 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.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

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. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
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.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING
First Named Inventor/Applicant Name:	Fabio TRENTO
Filer:	Kenneth B. Ma/Dwight Peck
Attorney Docket Number:	244168.000015US6

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Utility application filing	1011	1	280	280
Utility Search Fee	1111	1	600	600
Utility Examination Fee	1311	1	720	720
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**1600**

Electronic Acknowledgement Receipt

EFS ID:	24690459
Application Number:	15003327
International Application Number:	
Confirmation Number:	1097
Title of Invention:	COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING
First Named Inventor/Applicant Name:	Fabio TRENTO
Customer Number:	6980
Filer:	Kenneth B. Ma/Dwight Peck
Filer Authorized By:	Kenneth B. Ma
Attorney Docket Number:	244168.000015US6
Receipt Date:	21-JAN-2016
Filing Date:	
Time Stamp:	16:42:02
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$1600
RAM confirmation Number	3769
Deposit Account	201507
Authorized User	MA, KENNETH

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal of New Application	US6-PTO-ApplicationTransmittal.PDF	278412 9a44359427bd815931e888255232e6dac8c57649	no	2
Warnings:					
Information:					
2	Application Data Sheet	US6-PTO-ApplicationDataSheet.PDF	1829667 a100cf57bb58b4e002f736a0d20421cae18b77f7	no	10
Warnings:					
Information:					
3		US6-PTO-PreliminaryAmendment.PDF	61596 1808c1c4e51f71c2c9199ea112d12331906c8298	yes	5

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Preliminary Amendment	1	1
	Specification	2	2
	Claims	3	4
	Applicant Arguments/Remarks Made in an Amendment	5	5

Warnings:					
Information:					
4		US6-PTO-Specification-Original.PDF	1881027 d57b9b0a5aa2957d27e4fd0a99452e45ef75d857	yes	41

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Specification	1	28
	Claims	29	35

	Abstract		36	36	
	Drawings-only black and white line drawings		37	41	
Warnings:					
Information:					
5	Specification	US6-PTO-SPECIFICATION-Clean.PDF	390119 dc36ba135789ef8b68a1ff503f0ea79c436805c1	no	33
Warnings:					
Information:					
6	Specification	US6-PTO-SPECIFICATION-MarkedUp.PDF	397550 25110f671013262ae9dce46b07b52e828d5f5a6c	no	34
Warnings:					
Information:					
7	Oath or Declaration filed	US6-PTO-Declaration.PDF	303515 3396ab8346f749a19634fd9ed8bf855232125505	no	5
Warnings:					
Information:					
8	Power of Attorney	US6-PTO-POA.PDF	253025 f1be99f054da8366ba0874752406ad39372b99a9	no	3
Warnings:					
Information:					
9	Fee Worksheet (SB06)	fee-info.pdf	35461 17f96f0c86ba31e53f37de73760a864e514618a6	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	5430372		

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 a 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.

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 15/003,327

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			N/A	280
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	600
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	720
TOTAL CLAIMS (37 CFR 1.16(i))	13 minus 20 =	*			OR	x 80 =	0.00
INDEPENDENT CLAIMS (37 CFR 1.16(h))	2 minus 3 =	*				x 420 =	0.00
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).						0.00
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0.00
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	1600

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.

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

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
15/003,327	01/21/2016	1629	1600	244168.000015US6	13	2

CONFIRMATION NO. 1097

6980
TROUTMAN SANDERS LLP
600 Peachtree Street
Suite 5200
Atlanta, GA 30308

FILING RECEIPT



Date Mailed: 02/09/2016

Receipt is acknowledged of this non-provisional 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 APPLICANT, 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 Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections 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**

Inventor(s)

Fabio TRENTO, Pare, ITALY;
Sergio CANTOREGGI, Cagiallo, SWITZERLAND;
Giorgia ROSSI, Cernobbio, ITALY;
Roberta CANNELLA, Varese, ITALY;
Daniele BONADEO, Casalzuigno, ITALY;

Applicant(s)

Helsinn Healthcare SA, Lugano/Pazzallo, SWITZERLAND;

Assignment For Published Patent Application

Helsinn Healthcare SA, Lugano/Pazzallo, SWITZERLAND

Power of Attorney: The patent practitioners associated with Customer Number 06980

Domestic Priority data as claimed by applicant

This application is a CON of 14/069,970 11/01/2013
which is a CON of 13/077,462 03/31/2011 PAT 8623826
which is a CON of PCT/IB2010/003106 11/18/2010
which claims benefit of 61/262,470 11/18/2009
and claims benefit of 61/382,709 09/14/2010

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: 02/05/2016
The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 15/003,327**
Projected Publication Date: 05/19/2016
Non-Publication Request: No
Early Publication Request: No
Title

COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING

Preliminary Class

514

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.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

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 countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

SelectUSA

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 U.S. offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to promote and facilitate business investment. SelectUSA provides information assistance to the international investor community; serves as an ombudsman for existing and potential investors; advocates on behalf of U.S. cities, states, and regions competing for global investment; and counsels U.S. economic development organizations on investment attraction best practices. To learn more about why the United States is the best country in the world to develop

technology, manufacture products, deliver services, and grow your business, visit http://www.SelectUSA.gov or call +1-202-482-6800.

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

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/003,327	01/21/2016	Fabio TRENTO	244168.000015US6	1097

6980 7590 03/10/2016

TROUTMAN SANDERS LLP
600 Peachtree Street
Suite 5200
Atlanta, GA 30308

EXAMINER
WEBB, WALTER E

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
03/10/2016	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):

jim.schutz@troutmansanders.com
ryan.schneider@troutmansanders.com
patents@troutmansanders.com

Office Action Summary	Application No. 15/003,327	Applicant(s) TRENTO ET AL.	
	Examiner WALTER WEBB	Art Unit 1612	AIA (First Inventor to File) Status No

-- 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 *1/21/2016*.

☐ 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) *16-18,21,23-26 and 52-56* 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) *16-18,21,23-26 and 52-56* 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

The present application is being examined under the pre-AIA first to invent provisions.

Claim Objections

Claim 17 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The lower limit for the occupation has been set in independent claim 16. Dependent claim 17 sets different lower limit for the occupation and therefore fails to further limit. The Examiner recommends changing the limitation to 80% or more.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of pre-AIA 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 16, 17, 23, 24, 26 and 54 are rejected under pre-AIA 35 U.S.C. 102(b) as being anticipated by Reddy et al., (Supportive Cancer Therapy, 2006).

Reddy et al. teaches treatment of chemotherapy-induced nausea and vomiting (CINV) by administering a Neurokinin-1 (NK-1), in combination with the “standard of

care for highly emetogenic chemotherapy" 5-HT3 antagonist and dexamethasone (p. 141, 1st column, 2nd paragraph).

Reddy et al. teaches netupitant as a suitable NK-1 antagonist, at that time, undergoing clinical development for the treatment of CINV in patients with cancer (p. 140, 3rd column, 2nd paragraph; see also table at p. 141).

Reddy et al. anticipatory insofar as it teaches administering netupitant to a patient in need thereof, i.e. patients with chemotherapy-induced nausea and vomiting.

Claim Rejections - 35 USC § 103

The following is a quotation of pre-AIA 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under pre-AIA 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of pre-AIA 35 U.S.C. 103(c) and potential pre-AIA 35 U.S.C. 102(e), (f) or (g) prior art under pre-AIA 35 U.S.C. 103(a).

Claims 16-18, 21, 23-26 and 52-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reddy et al., (Supportive Cancer Therapy, 2006).

Reddy et al. teaches treatment of chemotherapy-induced nausea and vomiting (CINV) by administering a Neurokinin-1 (NK-1) Antagonist, i.e. aprepitant, in combination with the "standard of care for highly emetogenic chemotherapy" **5-HT3 antagonist** and **dexamethasone** (p. 141, 1st column, 2nd paragraph).

Because Reddy et al. teaches **netupitant** as a suitable NK-1 antagonist, it would have been obvious to use netupitant as the NK-1 antagonist in combination with 5-HT3 antagonist and dexamethasone, especially since success was found with another NK-1 antagonist, Casopitant, in combination with 5-HT3 antagonist and dexamethasone. Specifically, Reddy teaches **enhanced** treatment of CINV with the addition of aprepitant or casopitant.

The prior art teaches administering the NK-1 antagonist, 5-HT3 antagonist and dexamethasone "1-5 days after chemotherapy" (p. 141, 1st column, 2nd paragraph). The NK-1 antagonist on "day 1" and the 5-HT3 antagonist and dexamethasone "before chemotherapy" (p. 141, 2nd column, 2nd paragraph). The prior art teaches where the 5-HT3 antagonist is **palonosetron** (claim 27; see Abstract)

In regard to claimed dosages, it would have been obvious to optimize a dosing regimen for the dexamethasone and netupitant, since they are taught to be useful for treating nausea and vomiting. Accordingly, "where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges

by routine experimentation" (see MPEP 2144.05 IIA quoting *In re Aller*, 220 F.2d 454, 456 (105 USPQ 233)).

Furthermore, the recitation “wherein said netupitant occupies at least 80% of NK_1 receptors in the striatum” is interpreted as an inherent property of netupitant.

Nonstatutory Obvious-type 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 obviousness-type 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); and *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 a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

1) Claims 16-18, 21, 23-26, 52-56 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-25 of U.S. Patent No. 8,623,826. Although the claims at issue are not identical, they are not patentably distinct from each other because the both claim a method of treating nausea and vomiting by administering netupitant.

2) Claims 16-18, 21, 23-26, 52-56 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-62 of U.S. Patent No. 9,186,357. Although the claims at issue are not identical, they are not patentably distinct from each other because the both claim a method of treating nausea and vomiting by administering netupitant.

3) Claims 16-18, 21, 23-26, 52-56 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 9,271,975. Although the claims at issue are not identical, they are not patentably distinct from each other because the both claim a method of treating nausea and vomiting by administering netupitant.

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Walter E. Webb whose telephone number is (571) 270-3287. The examiner can normally be reached on 9:00am-5:00pm Tues-Thurs EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick F. Krass can be reached (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Walter E. Webb

/WALTER WEBB/

Primary Examiner, Art Unit 1612

Notice of References Cited	Application/Control No. 15/003,327	Applicant(s)/Patent Under Reexamination TRENTO ET AL.	
	Examiner WALTER WEBB	Art Unit 1612	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
	A	US-				
	B	US-				
	C	US-				
	D	US-				
	E	US-				
	F	US-				
	G	US-				
	H	US-				
	I	US-				
	J	US-				
	K	US-				
	L	US-				
	M	US-				

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Reddy et al., "Novel Neurokinin-1 Antagonists as Antiemetics for the Treatment of Chemotherapy-Induced Emesis." Supportive Cancer Therapy, April 1, 2006; vol. 3, no. 3, pp. 140-142.
	V	
	W	
	X	

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

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

BIB DATA SHEET

CONFIRMATION NO. 1097

SERIAL NUMBER	FILING or 371(c) DATE RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
15/003,327	01/21/2016	514	1612	244168.000015US6

APPLICANTS

Helsinn Healthcare SA, Lugano/Pazzallo, SWITZERLAND;

INVENTORS

Fabio TRENTO, Pare, ITALY;
Sergio CANTOREGGI, Cagiallo, SWITZERLAND;
Giorgia ROSSI, Cernobbio, ITALY;
Roberta CANNELLA, Varese, ITALY;
Daniele BONADEO, Casalzuigno, ITALY;

**** CONTINUING DATA ***************************

This application is a CON of 14/069,970 11/01/2013 PAT 9271975
which is a CON of 13/077,462 03/31/2011 PAT 8623826
which is a CON of PCT/IB2010/003106 11/18/2010
which claims benefit of 61/262,470 11/18/2009
and claims benefit of 61/382,709 09/14/2010

**** FOREIGN APPLICATIONS ***************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****

02/05/2016

Foreign Priority claimed ☐ Yes ☑ No 35 USC 119(a-d) conditions met ☐ Yes ☑ No Verified and Acknowledged /WALTER E WEBB/ Examiner's Signature	☐ Met after Allowance Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		ITALY	5	13	2

ADDRESS

TROUTMAN SANDERS LLP
600 Peachtree Street
Suite 5200
Atlanta, GA 30308
UNITED STATES

TITLE

COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING

FILING FEE RECEIVED		
1600	FEES: Authority has been given in Paper No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	130	netupitant	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2016/02/26 14:46
L2	216800	emesis or nausea or vomit or vimiting or chemotherapy	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2016/02/26 14:47
L3	83	l1 and l2	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2016/02/26 14:47

2/26/2016 2:54:29 PM
C:\Users\wwebb\Documents\EAST\Workspaces\15003327_Netupitant for Centrally Mediated Nausea and Vomiting.wsp

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15003327	TRENTO ET AL.
	Examiner	Art Unit
	WALTER WEBB	1612

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner
514	17.7	2/26/2016	WW

SEARCH NOTES		
Search Notes	Date	Examiner
Inventor Name Search on PALM	2/26/2016	WW
EAST Search History	2/26/2016	WW
NPL search terms: netupitant	2/26/2016	WW

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

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

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
15/003,327	01/21/2016	Fabio TRENTO	244168.000015US6

CONFIRMATION NO. 1097

PUBLICATION NOTICE

6980
TROUTMAN SANDERS LLP
600 Peachtree Street
Suite 5200
Atlanta, GA 30308



Title:COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING

Publication No.US-2016-0136162-A1
Publication Date:05/19/2016

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Office of Public Records. The Office of Public Records can be reached by telephone at (703) 308-9726 or (800) 972-6382, by facsimile at (703) 305-8759, by mail addressed to the United States Patent and Trademark Office, Office of Public Records, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently http://pair.uspto.gov/. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

Doc Code: PA..
Document Description: Power of Attorney

PTO/AIA/82B (07-13)
Approved for use through 11/30/2014. OMB 0651-0051
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 displays a valid OMB control number

POWER OF ATTORNEY BY APPLICANT

I hereby revoke all previous powers of attorney given in the application identified in either the attached transmittal letter or the boxes below.

Application Number	Filing Date

(Note: The boxes above may be left blank if information is provided on form PTO/AIA/82A.)

☑ I hereby appoint the Patent Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above: 140619

OR

☐ I hereby appoint Practitioner(s) named in the attached list (form PTO/AIA/82C) as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the patent application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above. (Note: Complete form PTO/AIA/82C.)

Please recognize or change the correspondence address for the application identified in the attached transmittal letter or the boxes above to:

☑ The address associated with the above-mentioned Customer Number

OR

☐ The address associated with Customer Number:

OR

Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Email			

I am the Applicant (if the Applicant is a juristic entity, list the Applicant name in the box):

Helsinn Healthcare SA

☐ Inventor or Joint Inventor (title not required below)

☐ Legal Representative of a Deceased or Legally Incapacitated Inventor (title not required below)

☑ Assignee or Person to Whom the Inventor is Under an Obligation to Assign (provide signer's title if applicant is a juristic entity)

☐ Person Who Otherwise Shows Sufficient Proprietary Interest (e.g., a petition under 37 CFR 1.46(b)(2) was granted in the application or is concurrently being filed with this document) (provide signer's title if applicant is a juristic entity)

SIGNATURE of Applicant for Patent

The undersigned (whose title is supplied below) is authorized to act on behalf of the applicant (e.g., where the applicant is a juristic entity).

Signature		Date (Optional)	
Name	Matteo Missaglia		
Title	GENERAL COUNSEL & CHIEF LEGAL OFFICER		

NOTE: Signature - This form must be signed by the applicant in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. If more than one applicant, use multiple forms.

☐ Total of forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. 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 3 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.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Doc Code: PA..
Document Description: Power of Attorney

PTO/AIA/82A (07-13)
Approved for use through 11/30/2014. OMB 0651-0031
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 displays a valid OMB control number.

TRANSMITTAL FOR POWER OF ATTORNEY TO ONE OR MORE REGISTERED PRACTITIONERS

NOTE: This form is to be submitted with the Power of Attorney by Applicant form (PTO/AIA/82B) to identify the application to which the Power of Attorney is directed, in accordance with 37 CFR 1.5, unless the application number and filing date are identified in the Power of Attorney by Applicant form. If neither form PTO/AIA/82A nor form PTO/AIA82B identifies the application to which the Power of Attorney is directed, the Power of Attorney will not be recognized in the application.

Application Number	15/005,674
Filing Date	01-25-2016
First Named Inventor	Waldo Mossi
Title	CRYSTALLINE AND AMORPHOUS FORMS OF PALONOSETRON HYDROCHLORIDE
Art Unit	1672
Examiner Name	CHU, YONG LIANG
Attorney Docket Number	

SIGNATURE of Applicant or Patent Practitioner

Signature	/Clark G. Sullivan/	Date (Optional)	
Name	Clark G. Sullivan	Registration Number	36,942
Title (if Applicant is a juristic entity)			
Applicant Name (if Applicant is a juristic entity)			

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. If more than one applicant, use multiple forms.

☑ *Total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. 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 3 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.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Doc Code: PA..
Document Description: Power of Attorney

PTO/AIA/82A (07-13)
Approved for use through 11/30/2014. OMB 0651-0031
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 displays a valid OMB control number.

TRANSMITTAL FOR POWER OF ATTORNEY TO ONE OR MORE REGISTERED PRACTITIONERS

NOTE: This form is to be submitted with the Power of Attorney by Applicant form (PTO/AIA/82B) to identify the application to which the Power of Attorney is directed, in accordance with 37 CFR 1.5, unless the application number and filing date are identified in the Power of Attorney by Applicant form. If neither form PTO/AIA/82A nor form PTO/AIA82B identifies the application to which the Power of Attorney is directed, the Power of Attorney will not be recognized in the application.

Application Number	11/877,722
Filing Date	10-24-2007
First Named Inventor	Daniele Bonadeo
Title	Dosage Forms of Palonosetron Hydrochloride Having Improved Stability and Bioavailability
Art Unit	1619
Examiner Name	KASSA, TIGABU
Attorney Docket Number	

SIGNATURE of Applicant or Patent Practitioner

Signature	/Clark G. Sullivan/	Date (Optional)	
Name	Clark G. Sullivan	Registration Number	36,942
Title (if Applicant is a juristic entity)			
Applicant Name (if Applicant is a juristic entity)			

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. If more than one applicant, use multiple forms.

☑ *Total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. 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 3 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.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Doc Code: PA..
Document Description: Power of Attorney

PTO/AIA/82A (07-13)
Approved for use through 11/30/2014. OMB 0651-0051
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 displays a valid OMB control number.

TRANSMITTAL FOR POWER OF ATTORNEY TO ONE OR MORE REGISTERED PRACTITIONERS

NOTE: This form is to be submitted with the Power of Attorney by Applicant form (PTO/AIA/82B) to identify the application to which the Power of Attorney is directed, in accordance with 37 CFR 1.5, unless the application number and filing date are identified in the Power of Attorney by Applicant form. If neither form PTO/AIA/82A nor form PTO/AIA82B identifies the application to which the Power of Attorney is directed, the Power of Attorney will not be recognized in the application.

Application Number	14/793,233
Filing Date	07-07-2015
First Named Inventor	Giorgio Calderari
Title	LIQUID PHARMACEUTICAL FORMULATIONS OF PALONOSETRON
Art Unit	1628
Examiner Name	GEMBEH, SHIRLEY V
Attorney Docket Number	

SIGNATURE of Applicant or Patent Practitioner

Signature	/Clark G. Sullivan/	Date (Optional)	
Name	Clark G. Sullivan	Registration Number	36,942
Title (if Applicant is a juristic entity)			
Applicant Name (if Applicant is a juristic entity)			

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. If more than one applicant, use multiple forms.

☑ *Total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. 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 3 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.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Doc Code: PA..
Document Description: Power of Attorney

PTO/AIA/82A (07-13)
Approved for use through 11/30/2014. OMB 0651-0051
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 displays a valid OMB control number.

TRANSMITTAL FOR POWER OF ATTORNEY TO ONE OR MORE REGISTERED PRACTITIONERS

NOTE: This form is to be submitted with the Power of Attorney by Applicant form (PTO/AIA/82B) to identify the application to which the Power of Attorney is directed, in accordance with 37 CFR 1.5, unless the application number and filing date are identified in the Power of Attorney by Applicant form. If neither form PTO/AIA/82A nor form PTO/AIA82B identifies the application to which the Power of Attorney is directed, the Power of Attorney will not be recognized in the application.

Application Number	14/855,564
Filing Date	09-16-2015
First Named Inventor	Giorgio Calderari
Title	LIQUID PHARMACEUTICAL FORMULATIONS OF PALONOSETRON
Art Unit	1628
Examiner Name	GEMBEH, SHIRLEY V
Attorney Docket Number	

SIGNATURE of Applicant or Patent Practitioner

Signature	/Clark G. Sullivan/	Date (Optional)	
Name	Clark G. Sullivan	Registration Number	36,942
Title (if Applicant is a juristic entity)			
Applicant Name (if Applicant is a juristic entity)			

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. If more than one applicant, use multiple forms.

☑ *Total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. 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 3 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.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Doc Code: PA..
Document Description: Power of Attorney

PTO/AIA/82A (07-13)
Approved for use through 11/30/2014. OMB 0651-0051
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 displays a valid OMB control number.

TRANSMITTAL FOR POWER OF ATTORNEY TO ONE OR MORE REGISTERED PRACTITIONERS

NOTE: This form is to be submitted with the Power of Attorney by Applicant form (PTO/AIA/82B) to identify the application to which the Power of Attorney is directed, in accordance with 37 CFR 1.5, unless the application number and filing date are identified in the Power of Attorney by Applicant form. If neither form PTO/AIA/82A nor form PTO/AIA82B identifies the application to which the Power of Attorney is directed, the Power of Attorney will not be recognized in the application.

Application Number	14/927,669
Filing Date	10-30-2015
First Named Inventor	Keith Lorimer
Title	Crystal Forms of Anamorelin
Art Unit	1625
Examiner Name	CHANG, CELIA C
Attorney Docket Number	

SIGNATURE of Applicant or Patent Practitioner

Signature	/Clark G. Sullivan/	Date (Optional)	
Name	Clark G. Sullivan	Registration Number	36,942
Title (if Applicant is a juristic entity)			
Applicant Name (if Applicant is a juristic entity)			

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. If more than one applicant, use multiple forms.

☑ *Total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. 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 3 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.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Doc Code: PA..
Document Description: Power of Attorney

PTO/AIA/82A (07-13)
Approved for use through 11/30/2014. OMB 0651-0031
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 displays a valid OMB control number.

TRANSMITTAL FOR POWER OF ATTORNEY TO ONE OR MORE REGISTERED PRACTITIONERS

NOTE: This form is to be submitted with the Power of Attorney by Applicant form (PTO/AIA/82B) to identify the application to which the Power of Attorney is directed, in accordance with 37 CFR 1.5, unless the application number and filing date are identified in the Power of Attorney by Applicant form. If neither form PTO/AIA/82A nor form PTO/AIA82B identifies the application to which the Power of Attorney is directed, the Power of Attorney will not be recognized in the application.

Application Number	15/003,327
Filing Date	01-21-2016
First Named Inventor	Fabio TRENTO
Title	COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING
Art Unit	1612
Examiner Name	WEBB, WALTER E
Attorney Docket Number	

SIGNATURE of Applicant or Patent Practitioner

Signature	/Clark G. Sullivan/	Date (Optional)	
Name	Clark G. Sullivan	Registration Number	36,942
Title (if Applicant is a juristic entity)			
Applicant Name (if Applicant is a juristic entity)			

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. If more than one applicant, use multiple forms.

☑ *Total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. 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 3 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.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Doc Code: PA..
Document Description: Power of Attorney

PTO/AIA/82A (07-13)
Approved for use through 11/30/2014. OMB 0651-0051
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 displays a valid OMB control number.

TRANSMITTAL FOR POWER OF ATTORNEY TO ONE OR MORE REGISTERED PRACTITIONERS

NOTE: This form is to be submitted with the Power of Attorney by Applicant form (PTO/AIA/82B) to identify the application to which the Power of Attorney is directed, in accordance with 37 CFR 1.5, unless the application number and filing date are identified in the Power of Attorney by Applicant form. If neither form PTO/AIA/82A nor form PTO/AIA82B identifies the application to which the Power of Attorney is directed, the Power of Attorney will not be recognized in the application.

Application Number	14/150,360
Filing Date	01-08-2014
First Named Inventor	Silvina GARCIA RUBIO
Title	ASYMMETRIC UREAS AND MEDICAL USES THEREOF
Art Unit	1625
Examiner Name	CHANG, CELIA C
Attorney Docket Number	

SIGNATURE of Applicant or Patent Practitioner

Signature	/Clark G. Sullivan/	Date (Optional)	
Name	Clark G. Sullivan	Registration Number	36,942
Title (if Applicant is a juristic entity)			
Applicant Name (if Applicant is a juristic entity)			

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. If more than one applicant, use multiple forms.

☑ *Total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. 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 3 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.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Doc Code: PA..
Document Description: Power of Attorney

PTO/AIA/82A (07-13)
Approved for use through 11/30/2014. OMB 0651-0051
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 displays a valid OMB control number.

TRANSMITTAL FOR POWER OF ATTORNEY TO ONE OR MORE REGISTERED PRACTITIONERS

NOTE: This form is to be submitted with the Power of Attorney by Applicant form (PTO/AIA/82B) to identify the application to which the Power of Attorney is directed, in accordance with 37 CFR 1.5, unless the application number and filing date are identified in the Power of Attorney by Applicant form. If neither form PTO/AIA/82A nor form PTO/AIA82B identifies the application to which the Power of Attorney is directed, the Power of Attorney will not be recognized in the application.

Application Number	14/351,113
Filing Date	04-10-2014
First Named Inventor	Claudio Pietra
Title	THERAPEUTIC COMBINATIONS OF NETUPITANT AND PALONOSETRON
Art Unit	1629
Examiner Name	HENLEY III, RAYMOND J
Attorney Docket Number	

SIGNATURE of Applicant or Patent Practitioner

Signature	/Clark G. Sullivan/	Date (Optional)	
Name	Clark G. Sullivan	Registration Number	36,942
Title (if Applicant is a juristic entity)			
Applicant Name (if Applicant is a juristic entity)			

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. If more than one applicant, use multiple forms.

☑ *Total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. 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 3 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.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Doc Code: PA..
Document Description: Power of Attorney

PTO/AIA/82A (07-13)
Approved for use through 11/30/2014. OMB 0651-0031
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 displays a valid OMB control number.

TRANSMITTAL FOR POWER OF ATTORNEY TO ONE OR MORE REGISTERED PRACTITIONERS

NOTE: This form is to be submitted with the Power of Attorney by Applicant form (PTO/AIA/82B) to identify the application to which the Power of Attorney is directed, in accordance with 37 CFR 1.5, unless the application number and filing date are identified in the Power of Attorney by Applicant form. If neither form PTO/AIA/82A nor form PTO/AIA82B identifies the application to which the Power of Attorney is directed, the Power of Attorney will not be recognized in the application.

Application Number	14/360,991
Filing Date	05-28-2014
First Named Inventor	Luca Fadini
Title	4-(5-(2-(3,5-BIS(TRIFLUOROMETHYL)PHENYL)-N,2-DIMETHYLPROPANAMIDO)-4-(o-TOLYL)PYRIDIN-2-YL)-1-METHYL-1-((PHOSPHONOOXY)METHYL)PIPERAZIN-1-IUM AS A NEUROKININ RECEPTOR MODULATOR
Art Unit	1624
Examiner Name	WILLIS, DOUGLAS M
Attorney Docket Number	

SIGNATURE of Applicant or Patent Practitioner

Signature	/Clark G. Sullivan/	Date (Optional)	
Name	Clark G. Sullivan	Registration Number	36,942
Title (if Applicant is a juristic entity)			
Applicant Name (if Applicant is a juristic entity)			

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. If more than one applicant, use multiple forms.

☑ *Total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. 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 3 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.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Doc Code: PA..
Document Description: Power of Attorney

PTO/AIA/82A (07-13)
Approved for use through 11/30/2014. OMB 0651-0051
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 displays a valid OMB control number.

TRANSMITTAL FOR POWER OF ATTORNEY TO ONE OR MORE REGISTERED PRACTITIONERS

NOTE: This form is to be submitted with the Power of Attorney by Applicant form (PTO/AIA/82B) to identify the application to which the Power of Attorney is directed, in accordance with 37 CFR 1.5, unless the application number and filing date are identified in the Power of Attorney by Applicant form. If neither form PTO/AIA/82A nor form PTO/AIA82B identifies the application to which the Power of Attorney is directed, the Power of Attorney will not be recognized in the application.

Application Number	13/865,649
Filing Date	04-18-2013
First Named Inventor	Shin-itsu Kuwabe
Title	Methods of Producing Anamorelin Hydrochloride Having Controlled Chloride Content
Art Unit	1625
Examiner Name	CHANG, CELIA C
Attorney Docket Number	

SIGNATURE of Applicant or Patent Practitioner

Signature	/Clark G. Sullivan/	Date (Optional)	
Name	Clark G. Sullivan	Registration Number	36,942
Title (if Applicant is a juristic entity)			
Applicant Name (if Applicant is a juristic entity)			

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. If more than one applicant, use multiple forms.

☑ *Total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. 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 3 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.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Doc Code: PA..
Document Description: Power of Attorney

PTO/AIA/82A (07-13)
Approved for use through 11/30/2014. OMB 0651-0031
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 displays a valid OMB control number.

TRANSMITTAL FOR POWER OF ATTORNEY TO ONE OR MORE REGISTERED PRACTITIONERS

NOTE: This form is to be submitted with the Power of Attorney by Applicant form (PTO/AIA/82B) to identify the application to which the Power of Attorney is directed, in accordance with 37 CFR 1.5, unless the application number and filing date are identified in the Power of Attorney by Applicant form. If neither form PTO/AIA/82A nor form PTO/AIA82B identifies the application to which the Power of Attorney is directed, the Power of Attorney will not be recognized in the application.

Application Number	14/539,318
Filing Date	11-12-2014
First Named Inventor	Shin-itsu Kuwabe
Title	Methods of Producing Anamorelin Hydrochloride Having Controlled Chloride Content
Art Unit	1625
Examiner Name	CHANG, CELIA C
Attorney Docket Number	

SIGNATURE of Applicant or Patent Practitioner

Signature	/Clark G. Sullivan/	Date (Optional)	
Name	Clark G. Sullivan	Registration Number	36,942
Title (if Applicant is a juristic entity)			
Applicant Name (if Applicant is a juristic entity)			

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. If more than one applicant, use multiple forms.

☑ *Total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. 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 3 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.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Doc Code: PA..
Document Description: Power of Attorney

PTO/AIA/82A (07-13)
Approved for use through 11/30/2014. OMB 0651-0051
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 displays a valid OMB control number.

TRANSMITTAL FOR POWER OF ATTORNEY TO ONE OR MORE REGISTERED PRACTITIONERS

NOTE: This form is to be submitted with the Power of Attorney by Applicant form (PTO/AIA/82B) to identify the application to which the Power of Attorney is directed, in accordance with 37 CFR 1.5, unless the application number and filing date are identified in the Power of Attorney by Applicant form. If neither form PTO/AIA/82A nor form PTO/AIA82B identifies the application to which the Power of Attorney is directed, the Power of Attorney will not be recognized in the application.

Application Number	15/135,051
Filing Date	04-21-2016
First Named Inventor	Shin-itsu Kuwabe
Title	Methods of Producing Anamorelin Hydrochloride Having Controlled Chloride Content
Art Unit	1625
Examiner Name	CHANG, CELIA C
Attorney Docket Number	

SIGNATURE of Applicant or Patent Practitioner

Signature	/Clark G. Sullivan/	Date (Optional)	
Name	Clark G. Sullivan	Registration Number	36,942
Title (if Applicant is a juristic entity)			
Applicant Name (if Applicant is a juristic entity)			

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. If more than one applicant, use multiple forms.

☑ *Total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. 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 3 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.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Doc Code: PA..
Document Description: Power of Attorney

PTO/AIA/82A (07-13)
Approved for use through 11/30/2014. OMB 0651-0051
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 displays a valid OMB control number.

TRANSMITTAL FOR POWER OF ATTORNEY TO ONE OR MORE REGISTERED PRACTITIONERS

NOTE: This form is to be submitted with the Power of Attorney by Applicant form (PTO/AIA/82B) to identify the application to which the Power of Attorney is directed, in accordance with 37 CFR 1.5, unless the application number and filing date are identified in the Power of Attorney by Applicant form. If neither form PTO/AIA/82A nor form PTO/AIA82B identifies the application to which the Power of Attorney is directed, the Power of Attorney will not be recognized in the application.

Application Number	15/135,107
Filing Date	04-21-2016
First Named Inventor	Shin-itsu Kuwabe
Title	Methods of Producing Anamorelin Hydrochloride Having Controlled Chloride Content
Art Unit	1625
Examiner Name	CHANG, CELIA C
Attorney Docket Number	

SIGNATURE of Applicant or Patent Practitioner

Signature	/Clark G. Sullivan/	Date (Optional)	
Name	Clark G. Sullivan	Registration Number	36,942
Title (if Applicant is a juristic entity)			
Applicant Name (if Applicant is a juristic entity)			

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. If more than one applicant, use multiple forms.

☑ *Total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. 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 3 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.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Doc Code: PA.,
Document Description: Power of Attorney

PTO/AIA/82A (07-13)
Approved for use through 11/30/2014. OMB 0651-0051
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 displays a valid OMB control number.

TRANSMITTAL FOR POWER OF ATTORNEY TO ONE OR MORE REGISTERED PRACTITIONERS

NOTE: This form is to be submitted with the Power of Attorney by Applicant form (PTO/AIA/82B) to identify the application to which the Power of Attorney is directed, in accordance with 37 CFR 1.5, unless the application number and filing date are identified in the Power of Attorney by Applicant form. If neither form PTO/AIA/82A nor form PTO/AIA82B identifies the application to which the Power of Attorney is directed, the Power of Attorney will not be recognized in the application.

Application Number	15/135,147
Filing Date	04-21-2016
First Named Inventor	Shin-itsu Kuwabe
Title	Methods of Producing Anamorelin Hydrochloride Having Controlled Chloride Content
Art Unit	1625
Examiner Name	CHANG, CELIA C
Attorney Docket Number	

SIGNATURE of Applicant or Patent Practitioner

Signature	/Clark G. Sullivan/	Date (Optional)	
Name	Clark G. Sullivan	Registration Number	36,942
Title (if Applicant is a juristic entity)			
Applicant Name (if Applicant is a juristic entity)			

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. If more than one applicant, use multiple forms.

☑ *Total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. 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 3 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.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Doc Code: PA..
Document Description: Power of Attorney

PTO/AIA/82A (07-13)
Approved for use through 11/30/2014. OMB 0651-0051
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 displays a valid OMB control number.

TRANSMITTAL FOR POWER OF ATTORNEY TO ONE OR MORE REGISTERED PRACTITIONERS

NOTE: This form is to be submitted with the Power of Attorney by Applicant form (PTO/AIA/82B) to identify the application to which the Power of Attorney is directed, in accordance with 37 CFR 1.5, unless the application number and filing date are identified in the Power of Attorney by Applicant form. If neither form PTO/AIA/82A nor form PTO/AIA82B identifies the application to which the Power of Attorney is directed, the Power of Attorney will not be recognized in the application.

Application Number	14/640,551
Filing Date	03-06-2015
First Named Inventor	Claudio Giuliano
Title	p-Substituted Asymmetric Ureas and Medical Uses Thereof
Art Unit	1624
Examiner Name	WILLIS, DOUGLAS M
Attorney Docket Number	

SIGNATURE of Applicant or Patent Practitioner

Signature	/Clark G. Sullivan/	Date (Optional)	
Name	Clark G. Sullivan	Registration Number	36,942
Title (if Applicant is a juristic entity)			
Applicant Name (if Applicant is a juristic entity)			

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. If more than one applicant, use multiple forms.

☑ *Total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. 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 3 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.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Doc Code: PA..
Document Description: Power of Attorney

PTO/AIA/82A (07-13)
Approved for use through 11/30/2014. OMB 0651-0031
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 displays a valid OMB control number.

TRANSMITTAL FOR POWER OF ATTORNEY TO ONE OR MORE REGISTERED PRACTITIONERS

NOTE: This form is to be submitted with the Power of Attorney by Applicant form (PTO/AIA/82B) to identify the application to which the Power of Attorney is directed, in accordance with 37 CFR 1.5, unless the application number and filing date are identified in the Power of Attorney by Applicant form. If neither form PTO/AIA/82A nor form PTO/AIA82B identifies the application to which the Power of Attorney is directed, the Power of Attorney will not be recognized in the application.

Application Number	14/839,038
Filing Date	08-28-2015
First Named Inventor	William MANN
Title	MEDICAL TREATMENTS BASED ON ANAMORELIN
Art Unit	1627
Examiner Name	JAVANMARD, SAHAR
Attorney Docket Number	

SIGNATURE of Applicant or Patent Practitioner

Signature	/Clark G. Sullivan/	Date (Optional)	
Name	Clark G. Sullivan	Registration Number	36,942
Title (if Applicant is a juristic entity)			
Applicant Name (if Applicant is a juristic entity)			

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. If more than one applicant, use multiple forms.

☑ *Total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. 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 3 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.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Doc Code: PA..
Document Description: Power of Attorney

PTO/AIA/82A (07-13)
Approved for use through 11/30/2014. OMB 0651-0051
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 displays a valid OMB control number.

TRANSMITTAL FOR POWER OF ATTORNEY TO ONE OR MORE REGISTERED PRACTITIONERS

NOTE: This form is to be submitted with the Power of Attorney by Applicant form (PTO/AIA/82B) to identify the application to which the Power of Attorney is directed, in accordance with 37 CFR 1.5, unless the application number and filing date are identified in the Power of Attorney by Applicant form. If neither form PTO/AIA/82A nor form PTO/AIA82B identifies the application to which the Power of Attorney is directed, the Power of Attorney will not be recognized in the application.

Application Number	14/839,038
Filing Date	08-28-2015
First Named Inventor	William MANN
Title	MEDICAL TREATMENTS BASED ON ANAMORELIN
Art Unit	1627
Examiner Name	JAVANMARD, SAHAR
Attorney Docket Number	

SIGNATURE of Applicant or Patent Practitioner

Signature	/Clark G. Sullivan/	Date (Optional)	
Name	Clark G. Sullivan	Registration Number	36,942
Title (if Applicant is a juristic entity)			
Applicant Name (if Applicant is a juristic entity)			

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. If more than one applicant, use multiple forms.

☑ *Total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. 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 3 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.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Doc Code: PA..
Document Description: Power of Attorney

PTO/AIA/82A (07-13)
Approved for use through 11/30/2014. OMB 0651-0051
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 displays a valid OMB control number.

TRANSMITTAL FOR POWER OF ATTORNEY TO ONE OR MORE REGISTERED PRACTITIONERS

NOTE: This form is to be submitted with the Power of Attorney by Applicant form (PTO/AIA/82B) to identify the application to which the Power of Attorney is directed, in accordance with 37 CFR 1.5, unless the application number and filing date are identified in the Power of Attorney by Applicant form. If neither form PTO/AIA/82A nor form PTO/AIA82B identifies the application to which the Power of Attorney is directed, the Power of Attorney will not be recognized in the application.

Application Number	14/842,250
Filing Date	09-01-2015
First Named Inventor	Ruben GIORGINO
Title	USE OF ELSIGLUTIDE TO TREAT GASTROINTESTINAL MUCOSITIS INCLUDING CHEMOTHERAPY-INDUCED DIARRHEA
Art Unit	1676
Examiner Name	LUKTON, DAVID
Attorney Docket Number	

SIGNATURE of Applicant or Patent Practitioner

Signature	/Clark G. Sullivan/	Date (Optional)	
Name	Clark G. Sullivan	Registration Number	36,942
Title (if Applicant is a juristic entity)			
Applicant Name (if Applicant is a juristic entity)			

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. If more than one applicant, use multiple forms.

☑ *Total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. 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 3 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.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Doc Code: PA..
Document Description: Power of Attorney

PTO/AIA/82A (07-13)
Approved for use through 11/30/2014. OMB 0651-0051
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 displays a valid OMB control number.

TRANSMITTAL FOR POWER OF ATTORNEY TO ONE OR MORE REGISTERED PRACTITIONERS

NOTE: This form is to be submitted with the Power of Attorney by Applicant form (PTO/AIA/82B) to identify the application to which the Power of Attorney is directed, in accordance with 37 CFR 1.5, unless the application number and filing date are identified in the Power of Attorney by Applicant form. If neither form PTO/AIA/82A nor form PTO/AIA82B identifies the application to which the Power of Attorney is directed, the Power of Attorney will not be recognized in the application.

Application Number	14/865,370
Filing Date	09-25-2015
First Named Inventor	Christian Bacilieri
Title	Crystalline Forms of an NK-1 Antagonist
Art Unit	1624
Examiner Name	BERNHARDT, EMILY A
Attorney Docket Number	

SIGNATURE of Applicant or Patent Practitioner

Signature	/Clark G. Sullivan/	Date (Optional)	
Name	Clark G. Sullivan	Registration Number	36,942
Title (if Applicant is a juristic entity)			
Applicant Name (if Applicant is a juristic entity)			

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. If more than one applicant, use multiple forms.

☑ *Total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. 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 3 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.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Doc Code: PA..
Document Description: Power of Attorney

PTO/AIA/82A (07-13)
Approved for use through 11/30/2014. OMB 0651-0031
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 displays a valid OMB control number.

TRANSMITTAL FOR POWER OF ATTORNEY TO ONE OR MORE REGISTERED PRACTITIONERS

NOTE: This form is to be submitted with the Power of Attorney by Applicant form (PTO/AIA/82B) to identify the application to which the Power of Attorney is directed, in accordance with 37 CFR 1.5, unless the application number and filing date are identified in the Power of Attorney by Applicant form. If neither form PTO/AIA/82A nor form PTO/AIA82B identifies the application to which the Power of Attorney is directed, the Power of Attorney will not be recognized in the application.

Application Number	62/311,573
Filing Date	03-22-2016
First Named Inventor	Claudio Giuliano
Title	Benzenesulfonyl-Asymmetric Ureas and Medical Uses Thereof
Art Unit	
Examiner Name	
Attorney Docket Number	

SIGNATURE of Applicant or Patent Practitioner

Signature	/Clark G. Sullivan/	Date (Optional)	
Name	Clark G. Sullivan	Registration Number	36,942
Title (if Applicant is a juristic entity)			
Applicant Name (if Applicant is a juristic entity)			

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. If more than one applicant, use multiple forms.

☑ *Total of ..... forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. 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 3 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.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Doc Code: PA..
Document Description: Power of Attorney

PTO/AIA/82A (07-13)
Approved for use through 11/30/2014. OMB 0651-0051
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 displays a valid OMB control number.

TRANSMITTAL FOR POWER OF ATTORNEY TO ONE OR MORE REGISTERED PRACTITIONERS

NOTE: This form is to be submitted with the Power of Attorney by Applicant form (PTO/AIA/82B) to identify the application to which the Power of Attorney is directed, in accordance with 37 CFR 1.5, unless the application number and filing date are identified in the Power of Attorney by Applicant form. If neither form PTO/AIA/82A nor form PTO/AIA82B identifies the application to which the Power of Attorney is directed, the Power of Attorney will not be recognized in the application.

Application Number	62/219,833
Filing Date	09-17-2015
First Named Inventor	Claudio Pietra
Title	THERAPEUTIC USES OF ELSIGLUTIDE
Art Unit	
Examiner Name	
Attorney Docket Number	

SIGNATURE of Applicant or Patent Practitioner

Signature	/Clark G. Sullivan/	Date (Optional)	
Name	Clark G. Sullivan	Registration Number	36,942
Title (if Applicant is a juristic entity)			
Applicant Name (if Applicant is a juristic entity)			

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. If more than one applicant, use multiple forms.

☑ *Total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. 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 3 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.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Doc Code: PA..
Document Description: Power of Attorney

PTO/AIA/82A (07-13)
Approved for use through 11/30/2014. OMB 0651-0031
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 displays a valid OMB control number.

TRANSMITTAL FOR POWER OF ATTORNEY TO ONE OR MORE REGISTERED PRACTITIONERS

NOTE: This form is to be submitted with the Power of Attorney by Applicant form (PTO/AIA/82B) to identify the application to which the Power of Attorney is directed, in accordance with 37 CFR 1.5, unless the application number and filing date are identified in the Power of Attorney by Applicant form. If neither form PTO/AIA/82A nor form PTO/AIA82B identifies the application to which the Power of Attorney is directed, the Power of Attorney will not be recognized in the application.

Application Number	62/237,839
Filing Date	10-06-2015
First Named Inventor	Luca FADINI
Title	CRYSTALLINE FORMS OF FOSNETUPITANT
Art Unit	
Examiner Name	
Attorney Docket Number	

SIGNATURE of Applicant or Patent Practitioner

Signature	/Clark G. Sullivan/	Date (Optional)	
Name	Clark G. Sullivan	Registration Number	36,942
Title (if Applicant is a juristic entity)			
Applicant Name (if Applicant is a juristic entity)			

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. If more than one applicant, use multiple forms.

☑ *Total of ..... forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. 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 3 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.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Electronic Acknowledgement Receipt

EFS ID:	25989292
Application Number:	15003327
International Application Number:	
Confirmation Number:	1097
Title of Invention:	COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING
First Named Inventor/Applicant Name:	Fabio TRENTO
Customer Number:	6980
Filer:	Clark G. Sullivan
Filer Authorized By:	
Attorney Docket Number:	244168.000015US6
Receipt Date:	07-JUN-2016
Filing Date:	21-JAN-2016
Time Stamp:	12:38:57
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Power of Attorney	Signed_US_POA.pdf	1912671 d093470db7f1cf4964ae49102ee58b75de9f6484	no	24

Warnings:

The page size in the PDF is too large. The pages should be 8.5 x 11 or A4. If this PDF is submitted, the pages will be resized upon entry into the Image File Wrapper and may affect subsequent processing	
Information:	
Total Files Size (in bytes):	1912671

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 a 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.

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
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.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	15003327
Filing Date	2016-01-21
First Named Inventor	Fabio TRENTO
Art Unit	1612
Examiner Name	Walter Webb
Attorney Docket Number	HHC002US6

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	5202333		1993-04-13	Berger et al.	
	2	5510486		1996-04-23	Robinson et al.	
	3	6297395		2001-10-03	Bos et al.	
	4	6719996		2004-04-13	Kuentz et al.	
	5	6593472		2003-07-15	Hoffmann et al.	

If you wish to add additional U.S. Patent citation information please click the Add button. Add

U.S.PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20090036459		2009-02-05	Andrews et al.	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	15003327
	Filing Date	2016-01-21
	First Named Inventor	Fabio TRENTO
	Art Unit	1612
	Examiner Name	Walter Webb
	Attorney Docket Number	HHC002US6

	2	20070009676		2007-08-30	Pfizer			
	3							

If you wish to add additional U.S. Published Application citation information please click the Add button. Add

FOREIGN PATENT DOCUMENTS Remove

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	2008049552	WO		2008-05-02	Helsinn Healthcare		
	2	2004067005	WO		2004-08-12	Helsinn Healthcare		
	3	2004073714	WO		2004-09-02	Helsinn Healthcare		

If you wish to add additional Foreign Patent Document citation information please click the Add button Add

NON-PATENT LITERATURE DOCUMENTS Remove

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, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	Japanese Office Action dated November 19, 2014, which issued during prosecution of Japanese Patent Application No. 2012-539433.	
	2	Torsten HOFFMANN, et al., "Design and synthesis of a novel, achiral class of highly potent and selective, orally active neurokinin-1 receoptor antagonists", Bioorganic & Medicinal Chemistry Letters 16 (2006) 1362-1365.	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	15003327
	Filing Date	2016-01-21
	First Named Inventor	Fabio TRENTO
	Art Unit	1612
	Examiner Name	Walter Webb
	Attorney Docket Number	HHC002US6

	3	European Search Report dated April 3, 2014, from corresponding European Application Number 14151676.5.	
	4	European Search Report dated March 25, 2014, from corresponding European Application Number 14151678.1.	
	5	European Search Report dated April 3, 2014, from corresponding European Application Number 14151683.1.	
	6	Press Release, GSK provides update on regulatory filings for Zunrisa/Rezonic; Issued: Monday 28 September 2009, London UK.	
	7	WARR 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. (2005) J. Clin. Oncol. 23(12):2822-2830.	
	8	HERRINGTON et al., 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. (2008) Cancer 112(9):2080-2087.	
	9	YEO 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. (2009) Breast Cancer Res. Treat. 113:529-535.	
	10	LONGO et al., Palonosetron plus 3-day aprepitant and dexamethasone to prevent nausea and vomiting in patients receiving highly emetogenic chemotherapy. (2011) Support Care Cancer 19:1159-1164.	
	11	Press Release, NK1 receptor antagonist by Roche; Issued: Thursday, 23 February 2006, httQ: Lfleaddiscoverirblogs2ot.com/2006/02/nk1-rece2tor-antagonist-b:1!:- roche.html (leaddiscovery.co.uk)	
	12	March 27, 2003, Approved FDA Prescribing Information for Emend	
	13	RUHLMANN, CHRISTINA et al., "Casopitant: a novel NK1-receptor antagonist in the prevention of chemotherapy-induced nausea and vomiting," Therapeutics and Clinical Risk Management, 2009:5 pp. 375-384	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	15003327
	Filing Date	2016-01-21
	First Named Inventor	Fabio TRENTO
	Art Unit	1612
	Examiner Name	Walter Webb
	Attorney Docket Number	HHC002US6

	14	PELLEGATII, MARIO et al., "Disposition and Metabolism of Radiolabeled Casopitant in Humans," Drug Metabolism O and Disposition, vol. 37, no. 8, 2009, pp.1635-1645
	15	HUANG, SHIH-CHUNG et al., "Neurokinin-1 receptor antagonists: a comprehensive patent survey," Expert Opin. Ther. 0 Patents (2010) 20(8), pp. 1019-1045
	16	REDDY, G. KESAVA et al., "Novel Neurokinin-1 Antagonists as Antiemetics for the Treatment of Chemotherapy-Induced Emesis," Supportive Cancer Therapy, April 1, 2006, LNKD-PUBMED: 18632487, vol. 3, no. 3, pp. 140-142, XP002626039, ISSN: 1543-2912
	17	DE WIT, R., "Current position of 5HT3 antagonists and the additional value of NK1 antagonists; a new class of antiemetics," British Journal of Cancer, June 16, 2003, LNKD-PUBMED: 12799621, vol. 88, no. 12, pp. 1823-1827, XP002626041, ISSN: 0007-0920
	18	DIEMUNSCH, P. et al., "Neurokinin-1 receptor antagonists in the prevention of postoperative nausea and vomiting," British Journal of Anaesthesia, July 2009, LNKD-PUBMED: 19454547, vol. 103, no. 1, pp. 7-13, XP002626040, ISSN: 1471-6771
	19	DIEMUNSCH, PIERRE et al., "Potential of Substance P Antagonists as Antiemetics," January 1,2003, Antiemetic Therapy, Basel [U.A.]: Karger, CH, pp. 78-97, XP008133831, ISBN: 978-3-8055-7547-8
	20	GRUNBERG, STEVEN M., 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: Official Journal of the Multinational Association of Supportive Care in Cancer, May 2009 LNKD-PUBMED: 19037667, vol. 17, no. 5, pp. 589-594, XP002626042, ISSN: 1433-7339
	21	STATHIS, MARIGO et al., "Inhibition of substance P-mediated responses in NG1 08-15 celis by netupitant and palonosetron exhibit synergistic effects," European Journal of Pharmacology 689 (2012) pp. 25-30

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

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

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	15003327
	Filing Date	2016-01-21
	First Named Inventor	Fabio TRENTO
	Art Unit	1612
	Examiner Name	Walter Webb
	Attorney Docket Number	HHC002US6

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Clark G. Sullivan/	Date (YYYY-MM-DD)	2016-06-10
Name/Print	Clark G. Sullivan	Registration Number	36,942

This collection of information is required by 37 CFR 1.97 and 1.98. 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 1 hour 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.**

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. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

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.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Patent Application Fee Transmittal

Application Number:	15003327
Filing Date:	21-Jan-2016
Title of Invention:	COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING
First Named Inventor/Applicant Name:	Fabio TRENTO
Filer:	Clark G. Sullivan
Attorney Docket Number:	244168.000015US6

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
		Total in USD ($)		**180**

Electronic Acknowledgement Receipt

EFS ID:	26031560
Application Number:	15003327
International Application Number:	
Confirmation Number:	1097
Title of Invention:	COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING
First Named Inventor/Applicant Name:	Fabio TRENTO
Customer Number:	6980
Filer:	Clark G. Sullivan
Filer Authorized By:	
Attorney Docket Number:	244168.000015US6
Receipt Date:	10-JUN-2016
Filing Date:	21-JAN-2016
Time Stamp:	14:53:26
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$180
RAM confirmation Number	061316INTEFSW14582001
Deposit Account	1009
Authorized User	Clark Sullivan

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		US6JUNE2016Amendment.pdf	889804 e9bfa71089e8853f03665e39bf9726239c83453c	yes	10
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Applicant Arguments/Remarks Made in an Amendment		1	1	
	Claims		2	4	
	Applicant Arguments/Remarks Made in an Amendment		5	10	
Warnings:					
Information:					
2	Transmittal Letter	US6JUNE2016IDS.pdf	51140 11af5f6d3f79638b491c6403bfb6ebff5f5b43db	no	1
Warnings:					
Information:					
3	Information Disclosure Statement (IDS) Form (SB08)	US6JUNE2016SB08.pdf	614500 a4103ad83966665485e69bfcfc384d30102a5302	no	6
Warnings:					
Information:					
A U.S. Publication Number Citation is required in the Information Disclosure Statement (IDS) form. You may remove the form to add the required data in order to correct the Informational Message or if you chose not to, the image of the form will be processed and be made available within the Image File Wrapper (IFW) system. However, no data will be extracted from this form. Any additional data such as Foreign Patent Documents or Non Patent Literature will be manually reviewed and keyed into USPTO systems.					
4	Non Patent Literature	EP_SearchReport1.PDF	364696 3648ca8e1d46c7f54340b464300005d6c422d197	no	7
Warnings:					
Information:					
5	Non Patent Literature	EP_Searchreport2.PDF	383312 b8070f3251027d822856b29e2e19391d99239b57	no	8
Warnings:					
Information:					

6	Non Patent Literature	EP_SearchReport3.PDF	528431 92b5cd7ee1827489051a98e14f993bbb8f99449e	no	10
Warnings:					
Information:					
7	Non Patent Literature	Hoffmann.pdf	207259 cf43148f7e9ff71b88ab4339d224cef8096da89d	no	4
Warnings:					
Information:					
8	Non Patent Literature	JP_OA.pdf	137160 c60c39c83ce851e4ae9b223c13632fe987bb427e	no	4
Warnings:					
Information:					
9	Fee Worksheet (SB06)	fee-info.pdf	30615 94dbf0ff262c3a3d45dd482b5f5f21e8e7792122	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	3206917		

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 a 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.

Docket No.: HHC002US6
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Trento et al.	)	Customer No.: 140619
Application No.: 15/003,327	)	Confirmation No.: 1097
Filing Date: 01-21-2016	)	Art Unit: 1612
For: COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING	)	Examiner: WEBB, WALTER E.

AMENDMENT AND RESPONSE TO OFFICE ACTION

Commissioner for Patents
Alexandria, VA 22313-1450

Dear Madam:

In response to the Office Action notified in the above-referenced application on March 10, 2016, please enter the following amendments and consider the following remarks.

A REPLACEMENT CLAIM SET begins on page 2.

REMARKS begin on page 5.

REPLACEMENT CLAIM SET

1)-15) (Canceled)

16) (Currently Amended) A method of treating nausea and vomiting from an emesis-inducing event for a period of five consecutive days in a patient in need thereof, comprising administering to said patient netupitant or a pharmaceutically acceptable salt thereof, in a therapeutically effective amount which is effective to treat nausea and vomiting during the acute and delayed phases of emesis, and which enters the systemic circulation, crosses the blood brain barrier and occupies ~~at least~~ 70% or more of NK_1 receptors in the striatum seventy-two hours after said administration, wherein said therapeutically effective dose comprises a single dose of netupitant or pharmaceutically acceptable salt thereof administered on day one of said five consecutive days.

17) (Currently amended) The method of claim 16, wherein said netupitant occupies ~~at least~~ 80% or more of NK_1 receptors in the striatum seventy-two hours after said administration.

18) (Previously Presented) The method of claim 16, further comprising: a) administering to said patient on day one a first dose of dexamethasone which is ineffective against nausea and vomiting when administered alone, but effective against nausea and vomiting when administered in combination with said netupitant, wherein said first dose comprises from 50 to 70% of a minimum effective dose when administered alone; and b) if said patient is subject to highly emetogenic chemotherapy, administering to said patient, on days two, three and four, a second dose of dexamethasone which is ineffective against nausea and vomiting when administered alone, but effective against nausea and vomiting when administered in combination with said netupitant, wherein said second dose comprises from 40 to 60% of a minimum effective dose when administered alone.

19) (Canceled)

20) (Canceled)

21) (Previously Presented) The method of claim 16 wherein: a) only one dose of netupitant is administered during said five days on day one, comprising about 300 mg. of netupitant as the free base; and b) administering about 12 mg. of dexamethasone on day one; and c) if

said patient is undergoing highly emetogenic chemotherapy, administering about 8 mg. of dexamethasone on days two, three and four.

22) (Canceled)

23) (Previously Presented) The method of claim 16 wherein said nausea and vomiting is chemotherapy induced nausea and vomiting ("CINV"), radiation therapy induced nausea and vomiting ("RINV"), or post-operative nausea and vomiting ("PONV").

24) (Previously Presented) The method of claim 16 wherein said nausea and vomiting is induced by moderately or highly emetogenic chemotherapy.

25) (Previously Presented) The method of claim 16 comprising administering moderately or highly emetogenic chemotherapy within from about one hour to about two hours of said administration of said netupitant or pharmaceutically acceptable salt thereof.

26) (Previously Presented) The method of claim 16 comprising treating nausea and vomiting in response to highly emetogenic chemotherapy during the acute phase, or in response to highly emetogenic chemotherapy during the delayed phase, or in response to moderately emetogenic chemotherapy during the acute phase, or in response to moderately emetogenic chemotherapy during the delayed phase.

27) -51) (Canceled)

52) (Previously Presented) The method of claim 16, comprising orally administering from about 200 to about 400 mg of netupitant as the free base.

53) (Previously Presented) The method of claim 16, comprising orally administering about 300 mg of netupitant as the free base.

54) (Currently Amended) A method of treating nausea and vomiting <u>in response to an emesis-inducing event</u> for a period of five consecutive days in a patient in need thereof, comprising administering to said patient netupitant or a pharmaceutically acceptable salt thereof, in a therapeutically effective amount which is effective to treat nausea and vomiting during the acute and delayed phases of emesis<u>, wherein said therapeutically effective amount of netupitant or pharmaceutically acceptable salt thereof is administered on day one of said five consecutive days</u>.

55) (Previously Presented) The method of claim 54, comprising orally administering from about 200 to about 400 mg of netupitant as the free base.

56) (Previously Presented) The method of claim 54, comprising orally administering about 300 mg of netupitant as the free base.

REMARKS

Status of Claims

After the amendment, claims 16-18, 21, 23-26, and 52-56 are pending. Independent claims 16 and 54 are amended to specify that the netupitant is administered only once on day one of the five consecutive day period. Support for the amendment can be found in the specification on page 12 subparagraph (i). Claim 17 is also amended for clarity, as suggested in the office action, to state that the netupitant occupies 70% or more of the NK1 receptors in the brain, rather than at least 70% of the NK1 receptors. No new matter is added by the amendment.

Claim Rejections – 35 U.S.C. § 112

The Office Action objected to the use of "at least 70%" in claim 17 for allegedly failing to limit the independent claim from which it depends. As kindly suggested by the Examiner, the claims have been amended to state "70% or more."

Claim Rejections – 35 U.S.C. § 102 and 103

The Office Action rejects all the pending claims as allegedly anticipated by or obvious over Reddy. Reddy is a general review discussing the development of NK1 antagonists such as aprepitant and netupitant for the treatment of chemotherapy induced nausea and vomiting. Reddy gives very little detail regarding the appropriate dosing regimen for these novel therapies, and gives absolutely no guidance on a suitable dosing regimen for netupitant. This is significant because all of the pending claims require that the netupitant be administered only once over a period of five consecutive days, during the acute and delayed phases of nausea. The claims describe a therapeutic regimen that is different in three critical respects from Reddy:

- A single administration of NK1 antagonist over a 5-day period;
- Efficacy from the NK1 antagonist during the acute phase; and
- Suitable doses for netupitant and dexamethasone in the therapeutic regimen.

Single dose limitation

While Reddy generally discusses the development of NK1 antagonists for CINV, his article focuses principally on the development of aprepitant – the first NK1 antagonist approved by FDA for the treatment of CINV. Merck Pharmaceuticals markets aprepitant as Emend® as part of a three drug therapeutic regimen that includes a corticosteroid such as dexamethasone and a 5HT3 antagonist such as ondansetron.

The FDA-approved prescribing information for aprepitant is of record herein as NPL reference 12 in an Information Disclosure Statement filed concurrently herewith. The front page of the prescribing information recites the following recommended dosing regimen for aprepitant:

> **---------- DOSAGE AND ADMINISTRATION ----------**
> Recommended Dosage for Prevention of Chemotherapy Induced Nausea and Vomiting (CINV) (2.1)
> - EMEND capsules in adults and pediatric patients 12 years of age and older: is 125 mg on Day 1 and 80 mg on Days 2 and 3.
> - EMEND for oral suspension in pediatric patients 6 months to less than 12 years of age or pediatric and adult patients unable to swallow capsules: see dosing recommendations in Table 3 in the Full Prescribing Information.
> - Administer EMEND 1 hour prior to chemotherapy on Days 1, 2, and 3. If no chemotherapy is given on Days 2 and 3, administer EMEND in morning.
> - See Full Prescribing Information for recommended dosages of concomitant dexamethasone and 5-HT_3 antagonist for HEC and MEC.

As can be seen, FDA recommends that aprepitant (Emend) be administered multiple times during a five-day period to achieve efficacy. This is very different than the single administration of netupitant recited in the pending claims.

Reddy does not anticipate or render obvious independent claims 16 and 54 because Reddy does not describe or suggest the administration of a single dose of netupitant over a five-day period. Given the need to administer aprepitant on multiple occasions, a worker of ordinary skill could not reasonably have expected to administer netupitant only once during a five day period and control nausea based on Reddy's teachings.

Efficacy During the Acute Phase

The claims also require that netupitant treat emesis during the acute phase (claim 16) and during a continuous 5-day period (claim 54). Once again, the main 5HT3 antagonist discussed by Reddy – aprepitant – does not achieve this effect, and would not have motivated a skilled worker to administer netupitant for the treatment of acute phase emesis. Table 5 from the instant specification, reproduced below, proves this point:

TABLE 5: COMPLETE RESPONSE RATE FOR THE OVERALL, ACUTE AND DELAYED PHASE: MFAS Population

Efficacy endpoint	Palo alone (n=136)	Palo + Netu 100 mg (n=135)	Palo + Netu 200 mg (n=137)	Palo + Netu 300 mg (n=135)	Aprepitant Regimen (N=134)
CR, Overall Phase, 0-120h					
Percent of Patients	76.5	87.4	87.6	89.6	86.6
Difference from Palo alone (%)		10.9	11.1	13.2	10.1
p-value (*)		0.018	0.017	0.004	0.027
CR, Acute Phase, 0-24h					
Percent of Patients	89.7	93.3	92.7	98.5	94.8
Difference from Palo alone (%)		3.6	3.0	8.8	5.1
p-value (*)		0.278	0.383	0.007	0.114
CR, Delayed Phase, 25-120h					
Percent of Patients	80.1	90.4	91.2	90.4	88.8
Difference from Palo alone (%)		10.2	11.1	10.2	8.7
p-value (*)		0.018	0.010	0.018	0.043

(*) p-value from logistic regression analysis, aprepitant p-value from post-hoc logistic regression analysis.

Table 5 reports the results of a study comparing palonosetron alone to three different combinations of netupitant and palonosetron, as well as the combination of aprepitant and ondansetron. By comparing the combination of palonosetron + netupitant to the single administration of palonoseton, one is able to determine whether netupitant is having an independent effect on the measured parameter.

In this case, the study was designed to determine whether the addition of netupitant to a palonosetron dosing regimen provided an additional benefit against emesis during the overall phase (0-120 hours), the acute phase (0-24 hours), and the delayed phase (25-120 hours). As can be seen, during the acute phase (0-24 hrs), the combination of palonsetron plus 300 mg netupitant was significantly better at controlling emesis than palonosetron alone (98.5% v. 89.7%), and

achieved statistical significance (p=0.007). In contrast, the aprepitant regimen improved the response rate only slightly (94.8% to 89.7%), and did not achieve statistical significance (0.117). Thus, while it can be said that netupitant prevents emesis during the acute phase, the same cannot be said for aprepitant.

Reddy does not anticipate or render obvious independent claims 16 and 54 because Reddy does not teach or suggest the prevention of emesis during the acute phase by netupitant. A worker of ordinary skill could not have expected this effect when the only marketed NK1 antagonist when this application was filed – aprepitant – failed to achieve this effect.

The dosing limitations

The Office Action states that the doses recited in the claims could have been arrived at via routine experimentation. This argument applies to the specific doses of netupitant recited in the claims and the sub-therapeutic dose of dexamethasone recited in the claims. Applicant respectfully disagrees with the rejection. A tremendous amount of work was required to discover these dosing limitations, including:

- A PET receptor occupancy study, which unexpectedly showed unique binding habits for netupitant to the NK1 receptor, and an extended period of binding to the NK1 receptor. Without this discovery, it would have been much more difficult to predict the efficacy of netupitant during an extended 5-day period, particularly when the only other approved NK1 antagonist (aprepitant) required multiple dosings.
- Applicant's discovery that the free base of netupitant was more suitable than a pharmaceutically acceptable salt. Without this discovery it would have been impossible to arrive at the 300 mg dose.
- Applicant's discovery that a sub-therapeutic dose of dexamethasone could be effective when added to a netupitant/palonosetron dosing regimen. Without this discovery, it would have been impossible to arrive at the sub-therapeutic dose of dexamethasone described in the claims.

The Examiner has not cited any prior art suggesting that any of these discoveries would have been made during the course of routine experimentation, and has not stated a prima facie case of obviousness.

Unexpected results

While Applicant disputes the existence of a prima facie case of obviousness, it nonetheless wishes to point out the significant unexpected results presented for netupitant in the specification. Applicant has unexpectedly observed (1) that only a single dose of netupitant is required during the acute and delayed phases of emesis, and (2) that netupitant also treats emesis during the acute phase.

These results are particularly significant because the closest prior art at the time of this application – an aprepitant/ondansetron dosing regimen approved for Emend® – required multiple doses during the 5-day period of acute and delayed emesis, and aprepitant does not have an independent effect during the acute phase. Both of these unexpected results are discussed in great detail above and are not repeated in this discussion. Applicant respectfully asserts that these results are unexpected, and that they independently support the patentability of the pending claims.

It is, however, worth mentioning the remarkable results the inventors obtained from their PET brain scan study, particularly given their relationship to these unexpected results. Example 5 reports this study. As can be seen, even in the smallest dose group (100 mg), greater than 70% of NK1 receptors in 4 of 6 brain regions were still occupied by netupitant 96 hours after netupitant administration. This long binding period probably accounts for the requirement for only a single administration of netupitant during a five-day period, and might also account for netupitant's efficacy during the acute phase. This unexpected result also independently supports the patentability of the claimed invention.

Non-statutory obviousness type double patenting

The Office Action also rejects the pending claims based on non-statutory obviousness-type double patenting over various previously granted patents in the same family as this one:

- U.S. 8,623,826
- U.S. 9,186,357
- U.S. 9,271,975

While Applicant respectfully disagrees with the rejection, Applicant is filing a suitable terminal disclaimer herewith out of a spirit of cooperation in order to have this application more promptly allowed.

CONCLUSION

It is respectfully submitted that the application is in condition for allowance. Should the Examiner have any questions or concerns regarding this application, the Examiner is invited to contact the undersigned at 404.483.9360.

Respectfully submitted,

By: /CLARK G. SULLIVAN/
Clark G. Sullivan
Reg. No. 36,942

June 10, 2016

Customer No. 140619
Attorney Docket No.: HHC002.US6

Docket No.: HHC002US6
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Trento et al.	)	Customer No.: 140619
Application No.: 15/003,327	)	Confirmation No.: 1097
Filing Date: 01-21-2016	)	Art Unit: 1612
For: COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING	)	Examiner: WEBB, WALTER E.

INFORMATION DISCLOSURE STATEMENT

Commissioner for Patents
Alexandria, VA 22313-1450

Dear Madam:

Filed currently herewith is a form SB08 in compliance with 37 C.F.R. §§ 1.56, 1.97 and 1.98. In accordance with section 1.98(a)(2)(ii), copies of published U.S. patents and U.S. patent publications are omitted. In accordance with section 1.98(d), copies of foreign patent documents and non-patent literature are omitted to the extent they were previously provided in U.S.S.N. 13/077,462, to which this application claims priority. Copies of any foreign patent documents and non-patent literature not previously provided in U.S.S.N. 13/077,462 are filed concurrently herewith. Should the Examiner have any questions or concerns regarding this application, the Examiner is invited to contact the undersigned at 404.483.9360.

Respectfully submitted,

By: /CLARK G. SULLIVAN/
Clark G. Sullivan
Reg. No. 36,942

June 10, 2016
Customer No. 140619
Attorney Docket No.: HHC002.US6

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. 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 displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 15/003,327	Filing Date 01/21/2016	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ 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).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT **06/10/2016**

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 13	Minus	** 20	= 0	X $80 =	0
Independent (37 CFR 1.16(h))	* 2	Minus	***3	= 0	X $420 =	0
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	0

AMENDMENT

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					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 number found in the appropriate box in column 1.

HSLIE
TIFFANY VINES

This collection of information is required by 37 CFR 1.16. 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 12 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.**
If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

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

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
15/003,327	01/21/2016	Fabio TRENTO	244168.000015US6

CONFIRMATION NO. 1097

POA ACCEPTANCE LETTER

140619
Sullivan IP Solutions, LLC
PO Box 2252
New York, NY 10163

OC00000083697043

Date Mailed: 06/17/2016

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 06/07/2016.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/mnguyen/

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

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
15/003,327	01/21/2016	Fabio TRENTO	244168.000015US6

CONFIRMATION NO. 1097

POWER OF ATTORNEY NOTICE

6980
TROUTMAN SANDERS LLP
600 Peachtree Street
Suite 5200
Atlanta, GA 30308

OC000000083697030

Date Mailed: 06/17/2016

NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 06/07/2016.

- The Power of Attorney to you in this application has been revoked by the applicant. Future correspondence will be mailed to the new address of record(37 CFR 1.33).

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/mnguyen/

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

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/003,327	01/21/2016	Fabio TRENTO	244168.000015US6	1097

140619 7590 09/01/2016

Sullivan IP Solutions, LLC
PO Box 2252
New York, NY 10163

EXAMINER
WEBB, WALTER E

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
09/01/2016	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):

clark@sullivanipsolutions.com
docketing@sullivanipsolutions.com

Office Action Summary	Application No. 15/003,327	Applicant(s) TRENTO ET AL.	
	Examiner WALTER WEBB	Art Unit 1612	AIA (First Inventor to File) Status No

-- 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 *6/10/2016*.

☐ 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) *16-18,21,23-26 and 52-56* 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) *16-18,21,23-26 and 52-56* 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 *6/10/2016*.

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

4) ☐ Other: _____.

DETAILED ACTION

The present application is being examined under the pre-AIA first to invent provisions.

Applicants' arguments, filed 6/10/2016, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 103--Previous

The following is a quotation of pre-AIA 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under pre-AIA 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of pre-AIA 35 U.S.C. 103(c) and potential pre-AIA 35 U.S.C. 102(e), (f) or (g) prior art under pre-AIA 35 U.S.C. 103(a).

Claims 16-18, 21, 23-26 and 52-56 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Reddy et al., (Supportive Cancer Therapy, 2006).

Reddy et al. teaches treatment of chemotherapy-induced nausea and vomiting (CINV) by administering a Neurokinin-1 (NK-1) Antagonist, i.e. aprepitant, in combination with the "standard of care for highly emetogenic chemotherapy" **5-HT3 antagonist** and **dexamethasone** (p. 141, 1st column, 2nd paragraph).

Because Reddy et al. teaches **netupitant** as a suitable NK-1 antagonist, it would have been obvious to use netupitant as the NK-1 antagonist in combination with 5-HT3 antagonist and dexamethasone, especially since success was found with another NK-1 antagonist, Casopitant, in combination with 5-HT3 antagonist and dexamethasone. Specifically, Reddy teaches **enhanced** treatment of CINV with the addition of aprepitant or casopitant.

The prior art teaches administering the NK-1 antagonist, 5-HT3 antagonist and dexamethasone "1-5 days after chemotherapy" (p. 141, 1st column, 2nd paragraph). The NK-1 antagonist on "day 1" and the 5-HT3 antagonist and dexamethasone "before chemotherapy" (p. 141, 2nd column, 2nd paragraph). The prior art teaches where the 5-HT3 antagonist is **palonosetron** (claim 27; see Abstract)

In regard to claimed dosages, it would have been obvious to optimize a dosing regimen for the dexamethasone and netupitant, since they are taught to be useful for treating nausea and vomiting. Accordingly, "where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges

by routine experimentation" (see MPEP 2144.05 IIA quoting *In re Aller*, 220 F.2d 454, 456 (105 USPQ 233)).

Furthermore, the recitation “wherein said netupitant occupies at least 80% of NK_1 receptors in the striatum” is interpreted as an inherent property of netupitant.

Nonstatutory Obvious-type 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 obviousness-type 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); and *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 a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

1) Claims 16-18, 21, 23-26, 52-56 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-25 of U.S. Patent No. 8,623,826. Although the claims at issue are not identical, they are not patentably distinct from each other because the both claim a method of treating nausea and vomiting by administering netupitant.

2) Claims 16-18, 21, 23-26, 52-56 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-62 of U.S. Patent No. 9,186,357. Although the claims at issue are not identical, they are not patentably distinct from each other because the both claim a method of treating nausea and vomiting by administering netupitant.

3) Claims 16-18, 21, 23-26, 52-56 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 9,271,975. Although the claims at issue are not identical, they are not patentably distinct from each other because the both claim a method of treating nausea and vomiting by administering netupitant.

Response to Arguments

i) Applicant argues that Reddy gives little detail on dosing and no guidance on a suitable dosing regimen for netupitant (p. 5). This article focusses primarily on aprepitant (p. 6). Reddy does not teach administration of a single dose over a five day period to control nausea (Id.).

The Examiner disagrees.

It must be remembered that "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results". KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 416 (2007). If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability." *Id.* at 417. Moreover, the obviousness analysis is not limited to the explicit disclosures in prior art

publications, but must also take account of what an ordinary artisan would reasonably infer from those disclosures." *Id.* at 418.

The prior art teaches administering NK-1 antagonist (aprepitant), 5-HT3 antagonist and dexamethasone "1-5 days after chemotherapy" (p. 141, 1st column, 2nd paragraph). The NK-1 antagonist on "day 1" and the 5-HT3 antagonist and dexamethasone "before chemotherapy" (p. 141, 2nd column, 2nd paragraph). Thus, it would have been obvious to administer netupitant on day one of five consecutive days. The familiarity of working with an NK-1 antagonist and its intended use make obvious the administration of netupitant, as claimed, based on the administration of other NK-1 antagonists, e.g. aprepitant.

ii) Applicant argues that acute phase treatment could not have been predicted to have been a suitable treatment since the combination of palonsetron and netupitant outperformed aprepitant regimen during the same phase (p. 7-8). Applicant shows Table 5 as evidence.

However, this table does not show proof that the person having ordinary skill in the art would not administer netupitant during an acute phase, i.e. within 0-24 hours of emesis. These data, according to the instant specification, show "the efficacy and safety of three single oral doses of netupitant combined with oral palonosetron and given with dexamethasone, versus oral palonosetron-alone given with dexamethasone (without netupitant) for the prevention of highly emetogenic chemotherapy (HEC)-induced nausea and vomiting.

Note, the Examiner was unable to find a discussion of aprepitant that would lead one to believe that the data here was meant to distinguish over aprepitant, especially since numbers were fairly similar.

iii) Applicant argues that the discovery that the unique binding habits for netupitnat to the NK-1 receptor, efficacy of the free base form of netupitant, or the sub-therapeutic dose of dexamethasone could not have been predicted by the prior art.

However, the issue here is whether it would have been obvious or expected to administer netupitant to a patient for treating emesis. The prior art answers that that in the affirmative.

The binding habit of netupitant is an inherent property of netupitant. Applicant claims use of a pharmaceutically acceptable salt form of Netupitant and there is no teaching away from the free base form in the prior art. The prior art specifically recognized the benefits of dexamethasone in combination therapy for treatment of highly emetogenic chemotherapy.

iv) Applicant further argues unexpected results, stating, "Applicant has unexpectedly observed (1) that only a single dose of netupitant is required during the acute and delayed phases of emesis, and (2) that netupitant also treats emesis during the acute phase (p. 9).

Initially the Examiner was unable to confirm in the disclosure that treatment during the acute phase was unexpected. As the Examiner understands, chemotherapy-

induced nausea and vomiting can be broadly categorized as acute or delayed and it is important to treat during the acute phase (within 24 hrs.) to control the delayed emesis. Therefore, artisan would have reasonably been expected to treat emesis during the acute phase.

In regard to “unexpected” results, the specification disclosed, “it has unexpectedly been discovered that netupitant is active against nausea, and that a single dose of netupitant is able treat nausea and vomiting in response to highly and moderate emetogenic chemotherapy for five consecutive days” and “[i]t has also been discovered, quite unexpectedly, that netupitant exhibits unique binding habits to NK1 receptors in the brain" (Specification at p. 4, Summary of the Invention).

The idea that netupitant is active against nausea was disclosed in the prior art (i.e. Reddy et al.) and the binding to NK1 receptors, an inherent feature of netupitant, was also discussed in the prior art cited by Applicant, i.e. Hoffmann et al. (Bio Med Chem Ltrs 2006) submitted with the IDS filed 6/10/2016.

However, administration of a single dose for five consecutive days was not disclosed in Reddy, but may also be construed as an inherent property of netupitant, especially since the prior art teaches administration to patients for treatment of chemotherapy-induced nausea and vomiting.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Walter E. Webb whose telephone number is (571) 270-3287. The examiner can normally be reached on 9:00am-5:00pm Tues-Thurs EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick F. Krass can be reached (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Walter E. Webb

/WALTER WEBB/

Primary Examiner, Art Unit 1612

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
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.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	15003327
Filing Date	2016-01-21
First Named Inventor	Fabio TRENTO
Art Unit	1612
Examiner Name	Walter Webb
Attorney Docket Number	HHC002US6

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	5202333		1993-04-13	Berger et al.	
	2	5510486		1996-04-23	Robinson et al.	
	3	6297395		2001-10-03	Bos et al.	
	4	6719996		2004-04-13	Kuentz et al.	
	5	6593472		2003-07-15	Hoffmann et al.	

If you wish to add additional U.S. Patent citation information please click the Add button. Add

U.S.PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20090036459		2009-02-05	Andrews et al.	

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /W.W./

Receipt date: 06/10/2016

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	15003327
Filing Date	2016-01-21
First Named Inventor	Fabio TRENTO
Art Unit	1612
Examiner Name	Walter Webb
Attorney Docket Number	HHC002US6

	2	20070009676		2007-08-30	Pfizer		
	3						

If you wish to add additional U.S. Published Application citation information please click the Add button. Add

FOREIGN PATENT DOCUMENTS Remove

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	2008049552	WO		2008-05-02	Helsinn Healthcare		
	2	2004067005	WO		2004-08-12	Helsinn Healthcare		
	3	2004073714	WO		2004-09-02	Helsinn Healthcare		

If you wish to add additional Foreign Patent Document citation information please click the Add button Add

NON-PATENT LITERATURE DOCUMENTS Remove

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, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	Japanese Office Action dated November 19, 2014, which issued during prosecution of Japanese Patent Application No. 2012-539433.	
	2	Torsten HOFFMANN, et al., "Design and synthesis of a novel, achiral class of highly potent and selective, orally active neurokinin-1 receoptor antagonists", Bioorganic & Medicinal Chemistry Letters 16 (2006) 1362-1365.	

Receipt date: 06/10/2016

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	15003327
Filing Date	2016-01-21
First Named Inventor	Fabio TRENTO
Art Unit	1612
Examiner Name	Walter Webb
Attorney Docket Number	HHC002US6

	3	European Search Report dated April 3, 2014, from corresponding European Application Number 14151676.5.
	4	European Search Report dated March 25, 2014, from corresponding European Application Number 14151678.1.
	5	European Search Report dated April 3, 2014, from corresponding European Application Number 14151683.1.
	6	Press Release, GSK provides update on regulatory filings for Zunrisa/Rezonic; Issued: Monday 28 September 2009, London UK.
	7	WARR 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. (2005) J. Clin. Oncol. 23(12):2822-2830.
	8	HERRINGTON et al., 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. (2008) Cancer 112(9):2080-2087.
	9	YEO 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. (2009) Breast Cancer Res. Treat. 113:529-535.
	10	LONGO et al., Palonosetron plus 3-day aprepitant and dexamethasone to prevent nausea and vomiting in patients receiving highly emetogenic chemotherapy. (2011) Support Care Cancer 19:1159-1164.
	11	Press Release, NK1 receptor antagonist by Roche; Issued: Thursday, 23 February 2006, http: Lfleaddiscoverirblogs2ot.com/2006/02/nk1-rece2tor-antagonist-b:1!:- roche.html (leaddiscovery.co.uk)
	12	March 27, 2003, Approved FDA Prescribing Information for Emend
	13	RUHLMANN, CHRISTINA et al., "Casopitant: a novel NK1 receptor antagonist in the prevention of chemotherapy-induced nausea and vomiting," Therapeutics and Clinical Risk Management, 2009:5 pp. 375-384

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /W.W./

Receipt date: 06/10/2016

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	15003327
Filing Date	2016-01-21
First Named Inventor	Fabio TRENTO
Art Unit	1612
Examiner Name	Walter Webb
Attorney Docket Number	HHC002US6

	14	PELLEGATTI, MARIO et al., "Disposition and Metabolism of Radiolabeled Casopitant in Humans," Drug Metabolism and Disposition, vol. 37, no. 8, 2009, pp.1635-1645
	15	HUANG, SHIH-CHUNG et al., "Neurokinin-1 receptor antagonists: a comprehensive patent survey," Expert Opin. Ther. Patents (2010) 20(8), pp. 1019-1045
	16	REDDY, G. KESAVA et al., "Novel Neurokinin-1 Antagonists as Antiemetics for the Treatment of Chemotherapy-Induced Emesis," Supportive Cancer Therapy, April 1, 2006, LNKD-PUBMED: 18632487, vol. 3, no. 3, pp. 140-142, XP002626039, ISSN: 1543-2912
	17	DE WIT, R., "Current position of 5HT3 antagonists and the additional value of NK1 antagonists: a new class of antiemetics," British Journal of Cancer, June 16, 2003, LNKD-PUBMED: 12799621, vol. 88, no. 12, pp. 1823-1827, XP002626041, ISSN: 0007-0920
	18	DIEMUNSCH, P. et al., "Neurokinin-1 receptor antagonists in the prevention of postoperative nausea and vomiting," British Journal of Anaesthesia, July 2009, LNKD-PUBMED: 19454547, vol. 103, no. 1, pp. 7-13, XP002626040, ISSN: 1471-6771
	19	DIEMUNSCH, PIERRE et al., "Potential of Substance P Antagonists as Antiemetics," January 1,2003, Antiemetic Therapy, Basel [U.A.]: Karger, CH, pp. 78-97, XP008133831, ISBN: 978-3-8055-7547-8
	20	GRUNBERG, STEVEN M., 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: Official Journal of the Multinational Association of Supportive Care in Cancer, May 2009 LNKD-PUBMED: 19037667, vol. 17, no. 5, pp. 589-594, XP002626042, ISSN: 1433-7339
	21	STATHIS, MARICO et al., "Inhibition of substance P-mediated responses in NG1-08-15 cells by netupitant and palonosetron exhibit synergistic effects," European Journal of Pharmacology 689 (2012) pp. 25-30

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature	/Walter Webb/	Date Considered	08/29/2016

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

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /W.W./

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15003327	TRENTO ET AL.
	Examiner	Art Unit
	WALTER WEBB	1612

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner
514	17.7	2/26/2016	WW

SEARCH NOTES		
Search Notes	Date	Examiner
Inventor Name Search on PALM	2/26/2016	WW
EAST Search History	2/26/2016	WW
NPL search terms: netupitant	2/26/2016	WW

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
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.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	15003327
Filing Date	2016-01-21
First Named Inventor	TRENTO et al.
Art Unit	1612
Examiner Name	Walter E. Webb
Attorney Docket Number	HHC002

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Patent citation information please click the Add button. Add

U.S.PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Published Application citation information please click the Add button. Add

FOREIGN PATENT DOCUMENTS Remove

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	2009-507933	JP		2009-02-26	Helsinn Healthcare SA	Corresponds to WO 2008049552 (previously cited)	X
	2	2007096763	WO		2007-08-30	PFIZER LIMITED	Corresponds to US 20090036459	☐
	3	2004045615	WO		2004-06-03	Helsinn Healthcare SA		☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	15003327
	Filing Date	2016-01-21
	First Named Inventor	TRENTO et al.
	Art Unit	1612
	Examiner Name	Walter E. Webb
	Attorney Docket Number	HHC002

	4	2011061622	WO	A1	2011-05-26	Helsinn Healthcare S.A.		☐

If you wish to add additional Foreign Patent Document citation information please click the Add button Add

NON-PATENT LITERATURE DOCUMENTS Remove

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, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	Press Release, GSK provides update on regulatory filings for Zunrisa/Rezonic; Issued: Monday 28 September 2009, London UK.	
	2	WARR 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. (2005) J. Clin. Oncol. 23(12):2822-2830.	
	3	HERRINGTON et al., 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. (2008) Cancer 112(9):2080-2087.	
	4	YEO 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. (2009) Breast Cancer Res. Treat. 113:529-535.	
	5	LONGO et al., Palonosetron plus 3-day aprepitant and dexamethasone to prevent nausea and vomiting in patients receiving highly emetogenic chemotherapy. (2011) Support Care Cancer 19:1159-1164.	
	6	Press Release, NK1 receptor antagonist by Roche; Issued: Thursday, 23 February 2006, http://leaddiscovery.blogspot.com/2006/02/nk1-receptor-antagonist-by-roche.html (leaddiscovery.co.uk)	
	7	March 27, 2003, Approved FDA Prescribing Information for Emend	
	8	RUHLMANN, CHRISTINA et al., "Casopitant: a novel NK1-receptor antagonist in the prevention of chemotherapy-induced nausea and vomiting," Therapeutics and Clinical Risk Management, 2009:5 pp. 375-384	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	15003327
	Filing Date	2016-01-21
	First Named Inventor	TRENTO et al.
	Art Unit	1612
	Examiner Name	Walter E. Webb
	Attorney Docket Number	HHC002

	9	PELLEGATII, MARIO et al., "Disposition and Metabolism of Radiolabeled Casopitant in Humans," Drug Metabolism 0 and Disposition, vol. 37, no. 8, 2009, pp.1635-1645
	10	HUANG, SHIH-CHUNG et al., "Neurokinin-1 receptor antagonists: a comprehensive patent survey," Expert Opin. Ther. 0 Patents (2010) 20(8), pp. 1019-1045
	11	REDDY, G. KESAVA et al., "Novel Neurokinin-1 Antagonists as Antiemetics for the Treatment of Chemotherapy-Induced Emesis," Supportive Cancer Therapy, April 1, 2006, LNKD-PUBMED: 18632487, vol. 3, no. 3, pp. 140-142, XP002626039, ISSN: 1543-2912
	12	DE WIT, R., "Current position of 5HT3 antagonists and the additional value of NK1 antagonists; a new class of antiemetics," British Journal of Cancer, June 16, 2003, LNKD-PUBMED: 12799621, vol. 88, no. 12, pp. 1823-1827, XP002626041, ISSN: 0007-0920
	13	DIEMUNSCH, P. et al., "Neurokinin-1 receptor antagonists in the prevention of postoperative nausea and vomiting," British Journal of Anaesthesia, July 2009, LNKD-PUBMED: 19454547, vol. 103, no. 1, pp. 7-13, XP002626040, ISSN: 1471-6771
	14	DIEMUNSCH, PIERRE et al., "Potential of Substance P Antagonists as Antiemetics," January 1,2003, Antiemetic Therapy, Basel [U.A.]: Karger, CH, pp. 78-97, XP008133831, ISBN: 978-3-8055-7547-8
	15	GRUNBERG, STEVEN M., 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: Official Journal of the Multinational Association of Supportive Care in Cancer, May 2009 LNKD-PUBMED: 19037667, vol. 17, no. 5, pp. 589-594, XP002626042, ISSN: 1433-7339
	16	STATHIS, MARIGO et al., "Inhibition of substance P-mediated responses in NG1 08- 15 celis by netupitant and palonosetron exhibit synergistic effects," European Journal of Pharmacology 689 (2012) pp. 25-30

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

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

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	15003327
	Filing Date	2016-01-21
	First Named Inventor	TRENTO et al.
	Art Unit	1612
	Examiner Name	Walter E. Webb
	Attorney Docket Number	HHC002

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Clark G. Sullivan/	Date (YYYY-MM-DD)	2016-09-15
Name/Print	Clark G. Sullivan	Registration Number	36942

This collection of information is required by 37 CFR 1.97 and 1.98. 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 1 hour 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.**

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. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

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.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
26 May 2011 (26.05.2011)

PCT

(10) International Publication Number
WO 2011/061622 A1

(51) International Patent Classification:
A61K 31/4178 (2006.01) *A61K 31/573* (2006.01)
A61K 31/473 (2006.01) *A61K 45/06* (2006.01)
A61K 31/496 (2006.01) *A61P 1/08* (2006.01)

(21) International Application Number:
PCT/IB2010/003106

(22) International Filing Date:
18 November 2010 (18.11.2010)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/262,470 18 November 2009 (18.11.2009) US
61/382,709 14 September 2010 (14.09.2010) US

(71) Applicant *(for all designated States except US)*: **HELSINN HEALTHCARE S.A.** [CH/CH]; Via Pian Scairola 9, CH-6912 Pazallo (CH).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **TRENTO, Fabio** [IT/IT]; Via Alla Valle, 20 B, I-22020 Pare Como (IT). **CANTOREGGI, Sergio** [CH/CH]; Via ai Ronchi, 37, CH-6943 Vezia (CH). **ROSSI, Giorgia** [IT/IT]; Via della Liberta, 1A, I-22012 Cernobbio Como (IT). **CANNELA, Roberta** [IT/IT]; Via Al Colle, 42, I-21100 Varese (IT). **BONADEO, Daniele** [IT/IT]; Via Ronco Capo Caccia, 32, I-21030 Casalzuigno Varese (IT). **BRAGLIA, Riccardo** [CH/CH]; Via Pian Scairolo 9, CH-6912 Lugano-Pazzalo (CH).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

(54) **Title**: COMPOSITIONS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING

(57) **Abstract**: Provided are compositions and methods for treating or preventing nausea and vomiting in patients undergoing chemotherapy, radiotherapy, or surgery.

WO 2011/061622 A1

COMPOSITIONS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims benefit of U.S. Provisional Application No. 61/262,470, filed November 18, 2009 and U.S. Provisional Application No. 61/382,709, filed September 14, 2010. Application Nos. 61/262,470 and 61/382,709 are hereby incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

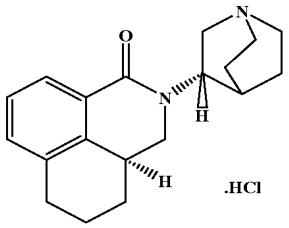
The present invention relates to the use of centrally acting NK_1 antagonists to treat nausea and vomiting, particular nausea and vomiting induced by highly emetogenic chemotherapy, and to the treatment of such nausea and vomiting over multiple consecutive days. The present invention also relates to combined oral dosage forms of palonosetron and netupitant.

BACKGROUND OF THE INVENTION

With the development of the 5-HT_3 antagonist in the early 1990s, there emerged new strategies in the medical community to better control nausea and vomiting caused by various medical procedures, including chemotherapy (CINV), surgery (PONV), and radiation therapy (RINV). When added to steroids such as dexamethasone, several 5-HT_3 antagonists have been demonstrated to significantly improve the standard of life for patients undergoing emetogenic medical procedures. Examples of 5-HT_3 antagonists include ondansetron, marketed by GlaxoSmithKline, and palonosetron, developed by Helsinn Healthcare.

Palonosetron hydrochloride has recently emerged as a highly efficacious anti-nauseant and anti-emetic agent. See PCT publications WO 2004/045615 and 2004/073714 from Helsinn Healthcare. Palonosetron hydrochloride is sold in the United States as a sterile injectable liquid under the ALOXI® brand, in sterile unit dose vials containing 0.075 or 0.25 mg. of palonosetron hydrochloride. Palonosetron hydrochloride also is also sold as an orally administered soft-gel dosage form containing 0.5 mg. of palonosetron hydrochloride.

The official chemical name for palonosetron hydrochloride is (3aS)-2-[(S)-l-Azabicyclo [2.2.2]oct-3-yl]- 2,3,3a,4,5,6-hexahydro-l-oxo-l*H*beriz[*de*] isoquinoline hydrochloride (CAS No. 119904-90-4); its empirical formula is $C_{19}H_{24}N_2O \cdot HCl$, and its molecular weight is 332.87. The compound is represented by the following chemical structure:

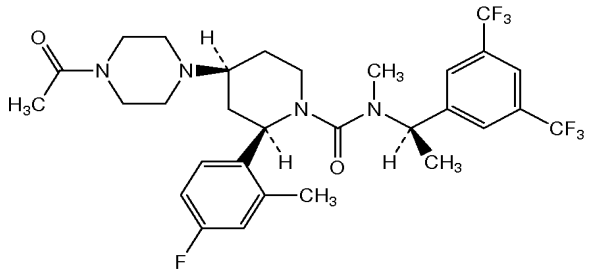


Methods of synthesizing palonosetron are described in U.S. Patent Nos. 5,202,333 and 5,510,486. Pharmaceutically acceptably dosage forms are described in PCT publications WO 2004/067005 and WO 2008/049552 from Helsinn Healthcare.

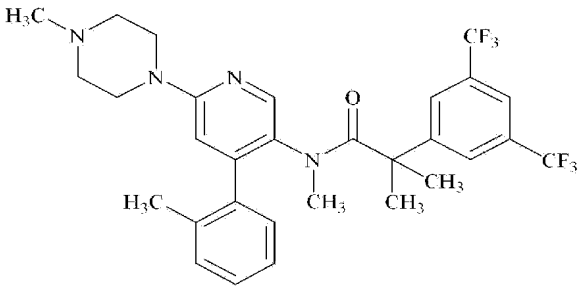
NK_1 antagonists have also recently emerged as a tool for combating nausea and vomiting from emetogenic medical procedures. Most recently, aprepitant was approved by the Food and Drug Administration ("FDA") for use in combination with other anti-emetic agents for the prevention of nausea and vomiting from moderately and highly emetogenic chemotherapy. However, it quickly became apparent that aprepitant's effect was limited principally to vomiting – not nausea – and that aprepitant did not provide as much benefit during the acute phase of CINV. When tested against nausea in humans, aprepitant was unable to induce a significant reduction in the incidence or severity of nausea following moderately or highly emetogenic chemotherapy when compared to a $5\text{-}HT_3$ antagonist alone. See FDA Approved Labeling for Emend®. Thus, while aprepitant is approved by FDA for the prevention of nausea and vomiting in humans, this indication is somewhat misleading because aprepitant did not reduce nausea in the clinical trials preformed for aprepitant more than nausea controlled by the other components of the anti-emetic regimen. In addition, the results reported in Grunberg *et al.*, SUPPORT CANCER CARE (2009) 17:589-594, from a combined treatment of aprepitant and palonosetron, were far from promising.

Merck & Co. markets aprepitant, as EMEND® in the United States. The product is approved in a capsule dosage form, and is marketed for the prevention of CINV (acute and delayed) in combination with other anti-emetic agents such as ondansetron and metoclopramide. The product reportedly has a terminal half-life of from 9 to 13 hours. While aprepitant has

demonstrated some effect against nausea, its effects have been inconsistent. Casopitant is another NK_1 antagonist that has been tested against nausea and vomiting in humans. A clinical study of casopitant is discussed in *Therapeutics and Clinical Risk Management* 2009:5 pp375-384 to Ruhlmann et al. and *Drug Metabolism and Disposition*, vol.37, No. 8, 2009, pp.1635-1645 to Pellegatti et al. As reported by Ruhlmann *et al.* in THERAPEUTICS AND CLINICAL RISK MANAGEMENT, 2009:5 375-384, casopitant had no statistically significant effect against nausea when administered in response to moderately emetogenic chemotherapy, and even induced nausea as a side effect. Casopitant has the formula (2*R*,4*S*)-4-(4-acetytlpiperazin-1-yl)-*N*-{(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethyl}-2-(4-fluoro-2-methylphenyl)-*N*-methylpiperidine-1-carboxamide, and the below chemical structure:



Netupitant is another selective NK_1 receptor antagonist under development by Helsinn Healthcare, having the formula 2-[3,5-bis(trifluoromethyl)phenyl]-N,2-dimethyl-N-[4-(2-methylphenyl)-6-(4-methylpiperazin-1-yl)pyridin-3-yl]propanamide, or Benzeneacetamide, N,α,α-trimethyl-N-[4-(2-methylphenyl)-6-(4-methyl-1-piperazinyl)-3-pyridinyl]-3,5-bis(trifluoromethyl)-, and the below chemical structure:



Methods of synthesizing and formulating netupitant and its prodrugs are described in U.S. Patent Nos. 6,297,375, 6,719,996 and 6,593,472 to Hoffmann La Roche.

Other representative NK_1 antagonists include ZD4974 (developed by AstraZeneca), CGP49823 (developed by Ciba-Geigy), Lanepitant and LY686017 (developed by Eli Lilly),

FK888 (developed by Fujisawa), Vofopitant, Vestipitant and Orvepitant (developed by GlaxoSmithKline), Befetupitant (developed by Hoffmann-La Roche), R116031 (developed by Janssen), L-733060 and L-736281 (developed by Merck), TKA731, NKP608 and DNK333 (developed by Novartis), CP-96345, CP-99994, CP-122721, CJ-17493, CJ-11974 and CJ-11972 (developed by Pfizer), RP67580 and Dapitant (developed by Rhone-Poulenc Rorer), Nolpitantium and SSR240600 (developed by Sanofi-Aventis), SCH388714 and Rolapitant (developed by Schering-Plough), TAK637 (developed by Takeda), HSP117 (developed by Hisamitsu), KRP103 (developed by Kyorin Pharm) and SLV317 (developed by Solvay). Chemical structures of the above-mentioned NK_1 antagonists are shown below and discussion of those compounds as well as other NK_1 antagonists is present in *Expert Opin. Ther. Patents* (2010) 20(8), pp1019-1045 by Huang et al.

The background of U.S. Patent No. 6,297,375 suggests that NK_1 antagonists are useful for treating a variety of conditions in which substance P (the natural ligand for the NK_1 receptor) is active. These conditions include depression, pain (especially pain resulting from inflammatory conditions such as migraine, rheumatoid arthritis, asthma, and inflammatory bowel disease), central nervous system (CNS) disorders such as Parkinson's disease and Alzheimer's disease, headache, anxiety, multiple sclerosis, attenuation of morphine withdrawal, cardiovascular changes, oedema, chronic inflammatory diseases such as rheumatoid arthritis, asthma/bronchial hyperreactivity and other respiratory diseases including allergic rhinitis, inflammatory diseases of the gut including ulcerative colitis and Crohn's disease, ocular injury and ocular inflammatory diseases. The background even mentions motion sickness and vomiting, but fails to call out nausea specifically.

Accordingly, there is a need in the art for more effective treatments of nausea and vomiting, particularly nausea and vomiting emanating from chemotherapy, radiotherapy and surgery. In addition, given the prolonged incidence of nausea and vomiting induced by these emetic events, there is a need for treating such nausea and vomiting for a prolonged period of time. Further, there is a need for the development of dosage forms to reduce drug-drug interaction, improve stability, and potentiate effects of each component of the combined dosage forms.

OBJECTS OF THE INVENTION

Accordingly, it is an object of the invention to provide new methods for treating or preventing nausea and vomiting using an NK_1 antagonist, particularly netupitant.

It is another object of the invention to provide methods for treating or preventing nausea and vomiting in patients undergoing chemotherapy, radiotherapy, or surgery.

Still another object of the invention is to augment existing treatments for CINV, RINV or PONV by steroids and 5-HT_3 antagonists, and thereby provide additional protection against both nausea and vomiting, especially during the acute and delayed phases.

Another object of the invention is to provide a single combined dose of netupitant and a 5-HT_3 antagonist and to the use of that single dose without further dosing, for the treatment of nausea and vomiting during the acute and delayed phases of CINV, RINV or PONV.

It is another object to provide novel methods to treat nausea, vomiting, and other undesirable effects from moderately emetogenic and highly emetogenic chemotherapy ("MEC and HEC"), especially HEC, during the acute and delayed phases following such treatments.

It is another object to provide novel dosage forms to reduce drug-drug interaction, improve stability, enhance bioavailability and potentiate therapeutic effect of each component of the combined dosage forms comprising netupitant and/or 5-HT_3 antagonist and/or dexamethasone, in treating or preventing nausea and vomiting.

SUMMARY OF THE INVENTION

After extensive testing into the clinical effects of netupitant, it has unexpectedly been discovered that netupitant is active against nausea, and that a single dose of netupitant is able to treat nausea and vomiting in response to highly and moderately emetogenic chemotherapy for five consecutive days. It has also been discovered, quite unexpectedly, that netupitant exhibits unique binding habits to NK_1 receptors in the brain. In particular, it has been discovered that netupitant binds to NK_1 receptors in the striatum in a long-lasting manner, and that less than 20 or 30% of netupitant is released from striatum NK_1 receptors even ninety-six hours after administration. This is in stark contrast to aprepitant, in which receptor binding drops swiftly over time, and must be dosed repeatedly if emesis control is desired throughout the delayed phase; and which shows no meaningful effect against nausea.

These discoveries have led to the development of a unique dosing regimen to treat nausea during the first day after an emesis-inducing event, in addition to the second, third, fourth and fifth days after such induction. Therefore, in one embodiment the invention provides a method of treating nausea and vomiting for a period of five consecutive days in a patient in need thereof, comprising administering to said patient netupitant or a pharmaceutically acceptable salt thereof in an amount which is therapeutically effective against nausea and vomiting during the acute and delayed phases, and which is effective to enter the systemic circulation, cross the blood brain barrier and occupy at least 70% of NK_1 receptors in the striatum seventy-two hours after said administration.

In another embodiment, the netupitant is combined with other anti-emetic agents, including a 5-HT_3 antagonist such as palonosetron and a corticosteroid such as dexamethasone, in a manner that results in even greater efficacy against nausea. It has been discovered that palonosetron is much more effective in combinations with netupitant than it is in combination with aprepitant, as reported by Grunberg et al., Support Cancer Care (2009) 17:589-594. In addition, palonosetron shows an improved pharmacokinetic profile (e.g., better bioavailability) when palonosetron is in combination with netupitant as opposed to palonosetron in single dose administration. Based on these discoveries, solid oral dosage forms have been developed that combine netupitant or another NK1 antagonist and palonosetron for the treatment of acute and delayed emesis.

It has also been discovered that netupitant potentiates the effect of dexamethasone, such that the dexamethasone is effective even when administered at sub-therapeutic doses (i.e. doses at which the dexamethasone would be ineffective if administered by itself). Therefore, in another embodiment the invention provides a combination therapy for treating nausea and vomiting for five consecutive days in a patient in need thereof, consisting essentially of:

- Day 1 netupitant -- administering to said patient on day one netupinant or a pharmaceutically acceptable salt thereof, in an amount which is therapeutically effective against nausea and vomiting during the acute and delayed phases, and which is effective to enter the systemic circulation, cross the blood brain barrier and occupy at least 70% of NK_1 receptors in the striatum seventy-two hours after said administration;
- Day 1 palonosetron -- administering to said patient on day one a therapeutically effective amount of a 5-HT_3 antagonist (preferably palonosetron) effective to treat said nausea and vomiting during the acute and delayed phases;

- Day 1 dexamethasone -- administering to said patient on day one a first dose of dexamethasone which is ineffective against nausea and vomiting when administered alone, but effective against nausea and vomiting when administered in combination with said netupitant and palonosetron, wherein said first dose comprises from 50 to 70% of a minimum effective dose when administered alone; and
- Days 2-5 dexamethasone – when the patient is undergoing highly emetogenic chemotherapy, administering to said patient, on days two, three and four, a second dose of dexamethasone which is ineffective against nausea and vomiting when administered alone, but effective against nausea and vomiting when administered in combination with said netupitant, wherein said second dose comprises from 40 to 60% of a minimum effective dose when administered alone on days two, three and four.

The dosage forms are extremely versatile and stable owing to their unique design and formulation. This versatility and stability is accomplished by formulating the NK1 antagonist and palonosetron in separate dosage forms and combining the dosage forms in one capsule. Thus, for example, the palonosetron can be formulated in a small gel-cap at a dose of around 0.5 mg, and the netupitant or other NK1 antagonist formulated in a tablet at a dose of about 100 to 150 mg. A capsule can then be filled with one or more palonosetron gel-caps and one or more netupitant (or other NK1 antagonist) tablets, depending on the therapeutic objective for the product. Because the palonosetron and NK1 antagonist are in separate dosage units, they can be formulated without regard to the stability of the other, and without degradation to by-products, for instance (3S)-3-[(3aS)-1-oxo- 2,3,3a,4,5,6-hexahydro-1*H*-benzo[*de*] isoquinoline-2-yl]-1-azoniabicyclo[2.2.2]octan-1-olate, a degradation by-product of palonosetron. As a result, the presently discovered dosage forms offer advantages, such as, reducing drug-drug interaction, improving stability, and potentiating effects of each component of the dosage forms in treating or preventing emesis.

Thus, in one embodiment the invention provides an orally administered dosage form comprising a combination of palonosetron and an NK1 antagonist (preferably netupitant), or a pharmaceutically acceptable salt or prodrug thereof.

In another embodiment the invention provides an orally administered capsule dosage form comprising (a) an outer shell; (b) one or more tablets housed within said outer shell, each comprising an NK1 antagonist (preferably netupitant) or a pharmaceutically acceptable salt or prodrug thereof and one or more pharmaceutically acceptable excipients; and (c) one or more soft-gel capsules housed within the outer shell, each comprising palonosetron or a pharmaceutically acceptable ester or prodrug thereof and one or more pharmaceutically

acceptable excipients; wherein said dosage form comprises (3S)-3-[(3aS)-1-oxo- 2,3,3a,4,5,6-hexahydro-1*H*-benzo[*de*] isoquinoline-2-yl]-1-azoniabicyclo[2.2.2]octan-1-olate in an amount that does not exceed 3 wt.%.

In still other embodiments the invention provides methods of treating acute and delayed-onset emesis by administering the dosage forms of the present invention to a human in need thereof, preferably shortly before the emesis inducing event.

Additional embodiments and advantages of the invention will be set forth in part in the description which follows, and in part will be obvious from the description, or may be learned by practice of the invention. The embodiments and advantages of the invention will be realized and attained by means of the elements and combinations particularly pointed out in the appended claims. It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as claimed.

BRIEF DESCRIPTION OF THE DRAWINGS

The accompanying drawings, which are incorporated in and constitute a part of this specification, illustrate several embodiments of the invention and together with the description, serve to explain the principles of the invention.

FIG. 1 depicts a capsule containing one soft-gel capsule of palonosetron and three tablets of netupitant.

FIG. 2 is a two dimensional graph plotting the pharmacokinetic profile of netupitant in humans following oral administration of netupitant alone and netupitant together with palonosetron.

FIG. 3 is a two dimensional graph plotting the pharmacokinetic profile of palonosetron in humans following oral administration of palonosetron alone and palonosetron together with netupitant.

FIG. 4 is a two dimensional graph plotting mean plasma concentrations of dexamethasone over time following administration with and without netupitant.

FIG. 5 contains two bar graphs that depict the average NK_1 receptor occupancy at 6, 24, 48, 72 and 96 hours after a single oral dose of 100, 300 and 450 mg. netupitant (N=2 for each dose) in striatum and occipital cortex, as measured using positron emission topography.

DETAILED DESCRIPTION OF THE INVENTION

The present invention may be understood more readily by reference to the following definitions and detailed description of preferred embodiments of the invention and the non-limiting Examples included therein.

Definitions and Use of Terms

When the singular forms "a," "an" and "the" or like terms are used herein, they will be understood to include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a pharmaceutical carrier" includes mixtures of two or more such carriers, and the like. The word "or" or like terms as used herein means any one member of a particular list and also includes any combination of members of that list.

When used herein the term "about" or "ca." will compensate for variability allowed for in the pharmaceutical industry and inherent in pharmaceutical products, such as differences in product strength and bioavailability due to manufacturing variations and time-induced product degradation. The term allows for any variation which in the practice of pharmaceuticals would allow the product being evaluated to be considered pharmaceutically equivalent or bioequivalent, or both if the context requires, to the recited strength of a claimed product.

Throughout the description and claims of this specification, the word "comprise" and variations of the word, such as "comprising" and "comprises," means "including but not limited to," and is not intended to exclude, for example, other additives, components, integers or steps.

As used herein, the term "Pharmaceutically acceptable" means that which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes that which is acceptable for veterinary use as well as human pharmaceutical use. In addition, the term "pharmaceutically acceptable salt" refers to a salt of a compound to be administered prepared from pharmaceutically acceptable non-toxic acids. Examples of suitable inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, sulfuric, and phosphoric. Suitable organic acids may be selected from aliphatic, aromatic, carboxylic and sulfonic classes of organic acids, examples of which are formic, acetic, propionic, succinic, camphorsulfonic, citric, fumaric, gluconic, isethionic, lactic, malic, mucic, tartaric, para-toluenesulfonic, glycolic, glucuronic, maleic, furoic, glutamic, benzoic, anthranilic,

salicylic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, pantothenic, benzenesulfonic (besylate), stearic, sulfanilic, alginic, galacturonic, and the like.

Pharmaceutically acceptable salts of palonosetron include palonosetron hydrochloride. Pharmaceutically acceptable pro-drugs of netupitant include those described in U.S. Patent Nos. 6,593,472, 6,747,026 and 6,806,370, including the N-oxide of netupitant. The contents of these publications are incorporated herein by reference. When a molecule is referred to herein in its base or salt form, it will be understand also to encompass other pharmaceutically acceptable salt forms of the molecule.

As used herein, "therapeutically effective amount" refers to an amount sufficient to elicit the desired biological response. The therapeutically effective amount or dose will depend on the age, sex and weight of the patient, and the current medical condition of the patient. The skilled artisan will be able to determine appropriate dosages depending on these and other factors in addition to the present disclosure.

The minimum effective dose of dexamethasone, when used to treat CINV induced by highly emetogenic chemotherapy, has been demonstrated to be 20 mg. administered orally or by injection on day one, and sixteen mg. administered orally or by injection on days two, three and four. Jordan *et al.*, THE ONCOLOGIST, Vol. 12, No. 9, 1143-1150, September 2007. When used to treat CINV induced by moderately emetogenic chemotherapy, the minimum effective dose of dexamethasone is 20 mg. administered orally or by injection on day one, and zero mg. on days two, three and four.

The terms "treating" and "treatment," when used herein, refer to the medical management of a patient with the intent to cure, ameliorate, stabilize, or prevent a disease, pathological condition, or disorder. This term includes active treatment, that is, treatment directed specifically toward the improvement of a disease, pathological condition, or disorder, and also includes causal treatment, that is, treatment directed toward removal of the cause of the associated disease, pathological condition, or disorder. In addition, this term includes palliative treatment, that is, treatment designed for the relief of symptoms rather than the curing of the disease, pathological condition, or disorder; preventative treatment, that is, treatment directed to minimizing or partially or completely inhibiting the development of the associated disease, pathological condition, or disorder; and supportive treatment, that is, treatment employed to

supplement another specific therapy directed toward the improvement of the associated disease, pathological condition, or disorder.

As used herein, the term "significantly" refers to a level of statistical significance. The level of statistical significant can be, for example, of at least $p<0.05$, of at least $p<0.01$, of at least $p<0.005$, or of at least $p<0.001$. Unless otherwise specified, the level of statistical significance is $p<0.05$. When a measurable result or effect is expressed or identified herein, it will be understood that the result or effect is evaluated based upon its statistical significance relative to a baseline. In like manner, when a treatment is described herein, it will be understood that the treatment shows efficacy to a degree of statistical significance.

5-HT_3 antagonists include the various setrons such as, for example, palonosetron, ondansetron, dolasetron, tropisetron, and granisetron, and their pharmaceutically acceptable salts. A preferred 5-HT_3 antagonist is palonosetron, especially its hydrochloride salt.

"Highly emetogenic chemotherapy" refers to chemotherapy having a high degree of emetogenic potential, and includes chemotherapy based on carmustine, cisplatin, cyclophosphamide $\geq$ 1500 mg/m^2, dacarbazine, dactinomycin, mechlorethamine, and streptozotocin.

"Moderately emetogenic chemotherapy" refers to chemotherapy having a moderate degree of emetogenic potential, and includes chemotherapy based on carboplatin, cyclophosphamide < 1500 mg/m^2, cytarabine > 1 mg/m^2, daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, and oxaliplatin.

Acute emesis refers to the first twenty-four hour period following an emesis-inducing event. Delayed emesis refers to the second, third, fourth and fifth twenty-four hour periods following an emesis-inducing event. When a treatment is said to be effective during the delayed phase, it will be understood to mean that the effectiveness of the treatment is statistically significant during the entire delayed phase, regardless of whether the treatment is effective during any particular twenty-four hour period of the delayed phase. It will also be understood that the method can be defined based upon its effectiveness during any one of the twenty-four hour periods of the delayed phase. Thus, unless otherwise specified, any of the methods of treating nausea and/or vomiting during the delayed phases, as described herein, could also be practiced to treat nausea and/or vomiting during the second, third, fourth or fifth twenty-four hour periods following an emesis inducing event, or an combination thereof.

When ranges are given by specifying the lower end of a range separately from the upper end of the range, it will be understood that the range can be defined by selectively combining any one of the lower end variables with any one of the upper end variables that is mathematically possible.

Methods of Treatment

As noted above, the invention is premised on several unique discoveries, and provides the following independent methods that can be practiced according to the present invention, including:

In a first principal embodiment, the invention provides a method of treating nausea and vomiting for a period of five consecutive days in a patient in need thereof, comprising administering to said patient netupitant or a pharmaceutically acceptable salt thereof in an amount which is therapeutically effective to treat nausea and vomiting during the acute and delayed phases, which enters the systemic circulation, crosses the blood brain barrier and occupies at least 70% of NK_1 receptors in the striatum seventy-two hours after said administration.

In a second principal embodiment, the invention provides a combination therapy for treating nausea and vomiting for five consecutive days in a patient in need thereof, comprising:

(i) administering to said patient on day one netupitant or a pharmaceutically acceptable salt thereof, in an amount which is therapeutically effective to treat nausea and vomiting during the acute and delayed phases, which enters the systemic circulation, crosses the blood brain barrier and occupies at least 70% of NK_1 receptors in the striatum seventy-two hours after said administration;

(ii) administering to said patient on day one a therapeutically effective amount of a 5-HT_3 antagonist (preferably palonosetron, more preferably 0.5 mg. of oral palonosetron as palonosetron hydrochloride) effective to treat said nausea and vomiting during the acute and delayed phases;

(iii) administering to said patient on day one a first dose of dexamethasone which is ineffective against nausea and vomiting when administered alone, but effective against nausea and vomiting when administered in combination with said netupitant and palonosetron, wherein said first dose comprises from 50 to 70% of a minimum effective dose when administered alone; and

(iv) if the patient is undergoing highly emetogenic chemotherapy, administering to said patient, on days two, three and four, a second dose of dexamethasone which is ineffective against nausea and vomiting when administered alone, but effective against nausea and vomiting

when administered in combination with said netupitant, wherein said second dose comprises from 40 to 60% of a minimum effective dose when administered alone on days two, three and four.

Various sub-embodiments are envisaged for these principal embodiments. For example, the netupitant can be administered as a free base or a pharmaceutically acceptable salt thereof, but is preferably administered as the free base. In addition, the netupitant is preferably administered in an amount ranging from about 50 to about 500 mg., from about 200 to about 400 mg., and preferably about 300 mg., based on the weight of the free base. A preferred route of administration for the netupitant is oral. In terms of binding to NK_1 receptors, the netupitant preferably binds to at least 80 or even 85% of NK_1 receptors in the striatum seventy-two hours after administration. As of ninety six hours after administration, the netupitant preferably binds less than 70, 60, 50 or even 40% of said NK_1 receptors.

The methods of the present invention are all effective at treating or preventing nausea and vomiting induced by numerous events, including chemotherapy induced nausea and vomiting ("CINV"), from moderately or highly emetogenic chemotherapy, radiation therapy induced nausea and vomiting ("RINV"), and post-operative nausea and vomiting ("PONV"). The method is preferably performed shortly before the emesis inducing event (i.e. no more than 1 or 2 hours before the event). The methods may be used to treat nausea and vomiting during the acute phase of emesis, or during the delayed phase.

The drugs specified by the individual embodiments may be administered by any suitable dosing regimen, as is well known in the art, but in a preferred embodiment the netupitant, 5-HT_3 antagonist and steroid are administered orally. A preferred oral dose of palonosetron ranges from about 0.075 to about 1.0 mg, or from about 0.25 to about 0.75 mg, but is preferably about 0.5 mg. A preferred oral dose of netupitant ranges from about 50 to 500 mg, or from about 200 to about 400 mg, but is preferably about 300 mg. A preferred dose of corticosteroid, preferably dexamethasone, is 12 mg administered orally or via injection on the first day of treatment, and 8 mg administered orally or via injection on the second, third and fourth days after said treatment.

It will be further understood that the netupitant can be administered in prodrug form, in which case the invention will provide a method of treatment by inducing plasma levels of netupitant, and in each case the plasma level of netupitant induced by the prodrug administration

will correspond to the level attained by the administration of netupitant or its pharmaceutically acceptable salt, in the doses and routes of administration described herein.

Pharmaceutical Compositions

Various pharmaceutical compositions can be developed that make use of the combinations described herein. The composition can be administered by any appropriate route, for example, orally, parenterally, or intravenously, in liquid or solid form.

Preferred modes of administrations of the active compounds are injectable and/or oral. These compositions will generally include an inert diluent or an edible carrier. They may be enclosed in gelatin capsules (for oral use) or compressed into tablets (for oral or buccal use) or formulated into troches (for buccal use). For these purposes, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition.

Tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a gliding such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring. When the dosage unit form is a capsule, it can contain, in addition to material of the above type, a liquid carrier such as a fatty oil. In addition, dosage unit forms can contain various other materials which modify the physical form of the dosage unit, for example, coatings of sugar, shellac, or other enteric agents.

The compounds can be administered as a component of an elixir, suspension, syrup, wafer, orally disintegrating film, orally disintegrating tablet, chewing gum or the like. A syrup may contain, in addition to the active compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors.

Solutions or suspensions used for injection can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates

and agents for the adjustment of tonicity such as sodium chloride, mannitol and dextrose. An injectable preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

Combined Oral Dosage Forms

As discussed above, the invention provides versatile combined oral dosage forms of palonosetron and an NK1 antagonist that can be readily modified depending on the therapeutic objective, and that do not present issues of stability and degradation. In a preferred embodiment, the invention provides a capsule for oral administration made from a hard outer shell that houses one or more NK1 antagonist tablets and one or more palonosetron soft-gel capsules. The finished capsule and the tablet(s) and soft-gel capsule(s) housed within the capsule shell are all preferably formulated as immediate release dosage forms. Netupitant and casopitant, and their pharmaceutically acceptable salts, are particularly preferred NK1 antagonists for the combined oral dosage forms of this invention.

While the NK1 antagonist is preferably formulated in a solid tablet, it will be understood that it can be formulated in any solid form that is suitable for oral administration including, for example, a tablet or capsule (hard or soft-gel). In a preferred embodiment, the NK1 antagonist is formulated in a tablet. The number of NK1 antagonist units contained within the combined dosage form can be, for example, from 1 to 10, 1 to 5, or 1 to 3. The netupitant units within the combined dosage form can provide anywhere from 50 to 500 mg of netupitant on an aggregate basis, preferably from 100 to 350 mg. Each netupitant unit preferably comprises from 50 to 200 mg of netupitant, more preferably 100 to 150 mg of netupitant, and most preferably 100 or 150 mg of netupitant.

The palonosetron can also be formulated in any solid form that is suitable for oral administration, although it is preferably formulated as a soft-gel capsule. Non-limiting examples of suitable palonosetron soft-gel capsules are provided in PCT publication WO 2008/049552, the contents of which are hereby incorporated by reference. The number of palonosetron units within the combined dosage from can be, for example, from 1 to 5, from 1 to 3 or just 1. Each of the palonosetron units within the combined dosage form can provide anywhere from 0.01 to 5.0 mg palonosetron, preferably from 0.1 to 1.0 mg palonosetron on an aggregate basis. Each

palonosetron unit will preferably comprise from 0.1 to 1.0 mg of palonosetron, most preferably about 0.25, 0.5, 0.75 or 1.0 mg of palonosetron.

Figure 1 illustrates an exemplary embodiment of a combined oral dosage form of palonosetron and netupitant. The dosage form 10 comprises a two piece hard outer shell that includes a body 20 and a cap 22. The dosage form 10 contains one palonosetron soft-gel capsule 30 (preferably containing 0.5 mg of palonosetron) and three netupitant tablets 40 (each preferably containing 100 mg of netupitant).

Hard Outer Shell

The hard outer shell of the present invention can be made of any pharmaceutically acceptable material that dissolves in gastric fluids. Preferred materials for the hard outer shell include, for example, gelatin, cellulose, starch, or hydroxypropyl methylcellulose (HPMC). In a particular embodiment of the invention, the hard outer shell has a maximum oxygen permeability. Preferably, the oxygen permeability is less about 1.0×10^{-3}, 5.0×10^{-4}, 1.0×10^{-4}, 5.0×10^{-5}, or even 2.0×10^{-5} ml·cm/(cm^2·24 hr. atm).

The hard outer shell can be a continuous structure. Alternatively, the hard outer shell can be a two-piece hard capsule.

Soft-Gel Capsule

The soft-gel capsule used for the palonosetron preferably comprises a soft outer shell and a liquid inner fill composition comprising palonosetron hydrochloride. Non-limiting examples of suitable palonosetron soft-gel capsules are provided in PCT publication WO 2008/049552, the contents of which are hereby incorporated by reference.

The soft outer shell of the soft-gel capsule can contain any type of material that dissolves in gastric fluids. Preferred materials for the soft outer shell include, for example, gelatin, cellulose, starch, or hydroxypropyl methylcellulose (HPMC). The soft-gel capsule can further comprise shell excipients such as glycerin, sorbitol, and colorants/opacifers such as titanium dioxide. The soft-gel capsule can further include solvents such as purified water. In particular embodiments of the invention, the outer shell has a maximum oxygen permeability, preferably of no more than 1.0×10^{-3}, 5.0×10^{-4}, 1.0×10^{-4}, 5.0×10^{-5}, or even 2.0×10^{-5} ml·cm/(cm^2·24 hr.

atm). Suitable soft-gel capsules include the 1.5-oval gelatine capsule shell manufactured by Catalent Pharma Solutions.

The liquid fill is preferably composed predominantly of one or more lipophilic components in an amount of from 50 wt.% to 99 wt.%, preferably from 75 wt.% to 98 wt.%. Preferred lipophilic components include, for example, mono- and di-glycerides of fatty acids, especially including the mono- and di-glycerides of capryl/capric acid. The liquid fill may also contain glycerin, preferably in an amount of from 1 to 15 wt.%, more preferably from 2 to 10 wt.%. In one preferred embodiment, both the shell and the inner fill composition comprise glycerin. In another preferred embodiment, the liquid fill comprises about 0.25, 0.50, 0.75 mg., or more of palonosetron as palonosetron hydrochloride.

The fill composition may comprise various means to facilitate the transition of palonosetron from the dosage form to the gastrointestinal fluids of the GI tract, so that the palonosetron may be more readily absorbed into the bloodstream. For example, the liquid fill composition may contain a surfactant, optimally in an amount of from 0.1 wt.% to 6 wt.%, from 0.5 wt.% to 5 wt.%, or from 1.0 wt.% to 3.0 wt.%. The liquid fill composition preferably comprises greater than 0.1, 0.5, or 1.0 wt.% of surfactant, and less than 10, 8, 5, 4, or even 4 wt.% of surfactant. A particularly preferred surfactant is polyglyceryl oleate.

Alternatively or in addition, the transitioning means for a liquid filled capsule may comprise water that forms a single phase or microemulsion with the other liquid ingredients in the excipient base. The liquid fill composition preferably comprises from 0.05 wt.% to 30 wt.% water, from 1 wt.% to 20 wt.% water, or from 2 wt.% to10 wt.% water. The liquid fill preferably comprises greater than 0.1, 0.5 or 1.0 wt.% water, and less than 20, 15, 10, 8 or 5 wt.% water.

The active agent, which is preferably palonosetron hydrochloride, is preferably present in the fill composition in an amount ranging from 0.01 to 10.0 wt.%, from 0.05 to 5.0 wt.%, or from 0.1 wt.% to 2.0 wt.%. Alternatively, particularly stable formulations have been found where the concentration of palonosetron exceeds 0.3%, preferably at a concentration no greater than 1 wt.%.

Tablet

The tablets of the present invention can include from 20 to 95 wt.% of NK1 antagonist (preferably netupitant), and preferably comprises from 60 to 80 wt.% of netupitant. In addition,

the tablets can contain diluents, disintegrants, surfactants, binders, glidants, and/or lubricants. In a particular embodiment, the tablet comprises from 5 to 25 wt.% of microcrystalline cellulose. The microcrystalline cellulose can function as a diluent and disintegrant, and preferably comprises 15 wt.% of the tablet. Another suitable disintegrant is sodium croscaramellose, which can be present in the tablet in an amount of from 1 to 5 wt.%, preferably 2 wt.%.

A suitable binder for use in the tablet is polyvinylpyrrolidone, which can be present in the tablet in an amount from 1 to 10 wt.% of the tablet, and preferably 5 wt.%. A suitable glidant for use in the tablet is colloidal silicon dioxide, which can be present in the tablet in an amount of 2 wt.%. Suitable lubricants for use in the tablet include sodium stearyl fumarate and magnesium stearate, which can be present in the tablet in an amount of 0.7 wt.% and 0.35 wt.%, respectively.

Application of The Combined Oral Dosage Forms

The invention further provides a method of treating emesis comprising orally administering to a patient suffering from emesis, or at risk for suffering emesis, a dosage form of the present invention. In still further embodiments, the invention provides methods of treating emesis by administering one or more of the dosage forms described herein. The dosage form is preferably administered shortly before the emesis inducing event (i.e. no more than 2 hours before the event). The emesis may be acute phase emesis (i.e. emesis experienced within about 24 hours of an emesis inducing event), or delayed emesis (i.e. emesis experienced after the acute phase, but within seven, six, five or four days of an emesis inducing event). The emesis may constitute chemotherapy induced nausea and vomiting ("CINV"), from moderately or highly emetogenic chemotherapy, radiation therapy induced nausea and vomiting ("RINV"), or post-operative nausea and vomiting ("PONV").

EXAMPLES

The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how the compounds claimed herein are made and evaluated, and are intended to be purely exemplary of the invention and are not intended to limit the scope of what the inventors regard as their invention. Efforts have been made to ensure accuracy with respect to numbers (e.g., amounts, temperature, etc.) but some errors and

deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, temperature is in °C or is at room temperature, and pressure is at or near atmospheric.

EXAMPLE 1 – PREPARATION OF ORAL DOSAGE FORM

In a preferred embodiment the combination is administered in a capsule oral dosage form, wherein the capsule houses one or more soft-gel capsules for the palonosetron and one or more hard tablets for the netupitant. Table 1 below describes a representative formulation for a soft-gel capsule containing 0.5 mg of palonosetron, suitable for inclusion in such a hard outer shell.

TABLE 1: REPRESENTATIVE SOFT-GEL FORMULATION

Ingredient	Approximate Amount (mg/Capsule)	Function
Fill Solution		
Palonosetron HCl	0.56[1]	Active
Mono- and di-glycerides of Capryl/Capric Acid (Capmul MCM)	62.19	Solvent vehicle
Glycerin, anhydrous, USP/Ph Eur	3.37	Plasticizer
Polyglyceryl oleate (Plurol Oleique CC 497)	0.87	Surfactant
Purified water, USP/Ph Eur	2.94	Co-solvent
Butylated hydroxyanisole (BHA), NF/Ph Eur	0.07	Antioxidant
Nitrogen	-	
Theoretical fill weight	70.00 mg	
Gelatine Capsule Shell, 1.5-oval (Catalent Pharma Solutions)[2]		
Gelatine (type 195), NF/Ph Eur	-	Shell
Sorbitol Special/Glycerin Blend 50/50	-	Plasticizer
Titanium dioxide, USP/Ph Eur	-	Colorant/Opacifier
Purified water, USP/Ph Eur	-	Solvent

[1]Corresponds to 0.50 mg. free base
[2]Quantitative composition of capsule shell is proprietary to Catalent Pharma Solutions

Table 2 below describes a representative formulation for a tablet containing 100 mg. of netupitant, suitable for inclusion in a hard shell.

TABLE 2: REPRESENTATIVE TABLET FORMULATION

Ingredient	Approximate Amount (mg/Tablet)	Function
Netupitant, milled	100	Active
Microcrystalline cellulose pH 101	20.5	Diluent and disintegrant
Sucrose Lauric Acid Esters	10.0	Surfactant
Polyvinilpyrrolidone K30	7.0	Binder
Sodium croscaramellose	3.0	Disintegrant
Colloidal Silicon Dioxide	3.0	Glidant
Sodium Stearyl Fumarate	1.0	Lubricant
Magnesium Stearate	0.5	Lubricant
Total weight	145 mg	

EXAMPLE 2 – PHARMACOKINETICS OF COMBINED DOSAGE FORM

Objective

The effects of palonosetron on the pharmacokinetics (PK) of netupitant and the effects of netupitant on the PK of palonosetron were examined in healthy volunteers.

Methods

A randomized, open, 3-way crossover study was conducted. Each subject participated in 3 treatment periods, each lasting approximately 12 days (Day -1 to Day 11). The treatment periods were separated by wash-out periods of no less than 14 days (between Day 1 of any 2 consecutive treatment periods).

The following treatments were investigated:

Treatment A: oral netupitant 450 mg. administered as single dose of three 150 mg. capsules.

Treatment B: oral palonosetron 0.75 mg. and oral netupitant 450 mg. administered simultaneously as three capsules of 150 mg. netupitant followed by 1 capsule of 0.75 mg. palonosetron.

Treatment C: oral palonosetron 0.75 mg. administered as single dose as one 0.75 mg. capsule.

Doses were administered under fasting conditions. Subjects fasted over-night for approximately 10 hours. Water, however, was permitted up to 1 hour pre-dose. Food intake was permitted 4 hours post-dose, and water was allowed ad libitum 1 hour post-dose.

Doses were administered with the subject in an upright position. The subjects remained in an upright position for 4 hours post-dose. The capsules were swallowed whole with 250 mL of room-temperature tap water. Repeated PK blood sampling (for netupitant and/or palonosetron) was performed.

Results

The primary PK variables assessed for netupitant and palonosetron were the maximum plasma concentration observed (C_{max}), the area under the plasma concentration versus time curve from time zero to the last quantifiable sampling time point (t) (AUC_{0-t}), and the area under the plasma concentration versus time curve from time zero to infinity (AUC_{0-inf}). The secondary PK variables assessed were the terminal elimination half-life ($t_{1/2,z}$), and the time at which the maximum plasma concentration was observed (t_{max}). Results are depicted in below Tables 3 and 4, as well as Figures 2 and 3.

Table 3: Summary of Netupitant Pharmacokinetic Parameters

Parameter	Netupitant 450 mg	Palonosetron 0.75 mg + Netupitant 450 mg
AUC_{0-t} [h*µg/L]	22808 (7270)	22775 (10064)
AUC_{0-inf} [h*µg/L]	25927 (10156)	26241 (13219)
C_{max} [µg/L]	650.2 (257.8)	659.7 (325.7)
t_{max} (h)	4.50 (3.00 ; 24.00)	4.50 (3.00 ; 23.95)
$t_{½,z}$ (h)	71.81 (37.10 ; 261.61)	78.31 (50.17 ; 196.13)

Mean and SD are shown, except for t_{max} and $t_{½}$, where median and range are shown.

As can be seen in Table 4 below, palonosetron shows a better pharmacokinetic profile when combined with Netupitant as opposed to administered as a single dose of palonosetron, for example, the greater AUC, the larger C_{max}, the shorter t_{max} (the median t_{max} was 0.5 hour shorter after administration of palonosetron in combination with netupitant), and the longer $t_{½,z}$.

Table 4: Summary of Palonosetron Pharmacokinetic Parameters

Parameter	Palonosetron 0.75 mg	Palonosetron 0.75 mg + Netupitant 450 mg
AUC_{0-t} [h*µg/L]	67415 (19554)	74230 (24866)
AUC_{0-inf} [h*µg/L]	70813 (20415)	77254 (25402)
C_{max} [µg/L]	1638.4 (415.5)	1863.1 (487.1)
t_{max} (h)	5.02 (4.00 ; 8.00)	4.50 (3.00 ; 6.02)
$t_{½,z}$ (h)	34.73 (19.61 ; 70.46)	36.91 (20.23 ; 56.08)

Mean and SD are shown, except for t_{max} and $t_{½}$, where median and range are shown.

EXAMPLE 3: NETUPITANT + DEXAMETHASONE DRUG INTERACTION STUDY

The effect of netupitant on orally administered dexamethasone pharmacokinetics was evaluated in this study. This was a randomized, open, 3-period crossover study utilizing an incomplete Latin Square design where subjects were given dexamethasone alone, or oral Netupitant 100 mg., 300 mg. or 450 mg. each given with dexamethasone. Netupitant was given orally on Day 1 only. The dexamethasone regimen for each treatment was 20 mg. orally Day 1, followed by 8 mg. orally every 12 hours from Day 2 through Day 4. Nineteen subjects (12 male and 7 female) completed the study (i.e., all 3 treatment periods).

Mean plasma concentrations of dexamethasone were higher when dexamethasone was co-administered with netupitant (Figure 4). The increase appeared to be dependant on the netupitant exposure.

The AUC_{0-24} (Day 1) of dexamethasone increased 1.5, 1.7 and 1.8-fold with co-administration of 100, 300 and 450 mg. netupitant, respectively. The AUC_{24-36} (Day 2) of dexamethasone increased 2.1, 2.4 and 2.6-fold and AUC_{84-108} and AUC_{84-inf} (Day 4) increased 1.7, 2.4 and 2.7-fold, with co-administration of 100, 300 and 450 mg. netupitant, respectively. Dexamethasone C_{max} on Day 1 was only slightly affected by co-administration of netupitant (1.1-fold increase during co-administration with 100 and 300 mg. netupitant, respectively, and 1.2-fold increase during co-administration with 450 mg. netupitant). C_{max} on Day 2 and Day 4 was increased approximately 1.7-fold in subjects administered netupitant. Dexamethasone C_{min} on Days 2-4 was increased approximately 2.8, 4.3 and 4.6-fold with co-administration of 100, 300 and 450 mg. netupitant, respectively. This clearly shows that the co-administration of netupitant and dexamethasone enhances the bioavailability of dexamethasone and provides a better therapeutic window of dexamethasone.

EXAMPLE 4: NETUPITANT PET RECEPTOR OCCUPANCY STUDY

This was a randomized, open-label, positron emission tomography (PET) study using 11C-GR205171 as tracer in 6 healthy male volunteers (2 per dose level) receiving single doses of netupitant (100, 300 or 450 mg) to investigate the degree of occupancy of NK_1 receptors in human brain, and to determine the relationship between plasma concentration of netupitant and NK_1 receptor occupancy (RO).

The anticipated high NK_1-RO (90% or higher) close to the expected C_{max} (6 hours post dose) was reached for striatum, occipital cortex, frontal cortex and anterior cingulate in 3 of 6 subjects of whom 1 received 300 mg. and 2 received 450 mg. of netupitant as a single oral dose.

All doses showed a relatively long duration of blockade of NK_1 receptors and the decline over time was dose dependent. In the 100 mg. dose group, 4 of 6 regions still had a mean NK_1-RO over 70% at 96 hours post dose. In the highest dose group (450 mg), 5 of 6 regions had a mean NK_1-RO of 80% or higher at 96 hours post dose. A comparison of the results for the dose groups (100 mg., 300 mg. and 450 mg) showed a consistent but small increase in NK_1-ROs with increasing netupitant dose. (Figure 5)

EXAMPLE 5: CLINICAL EFFICACY STUDY

A phase 2 trial evaluated three single doses of netupitant combined with palonosetron and dexamethasone compared to palonosetron alone and dexamethasone to obtain dose ranging information for netupitant used with oral palonosetron in the CINV patient population.

The objective of the study was to compare the efficacy and safety of three single oral doses of netupitant combined with oral palonosetron and given with dexamethasone, versus oral palonosetron-alone given with dexamethasone (without netupitant) for the prevention of highly emetogenic chemotherapy (HEC)-induced nausea and vomiting. The FDA-approved oral aprepitant regimen given with IV ondansetron and dexamethasone was included in the study as an active comparator for exploratory purposes. The FDA-approved oral palonosetron 0.5 mg. dose was used in each applicable treatment group in this study.

This was a multicenter, randomized, double-blind, double-dummy, parallel group, stratified study. Eligible patients were randomized (stratified by gender) to one of the following treatment groups:

Group 1 – 0.5 mg. oral palonosetron on Day 1 (with an oral dexamethasone standard regimen: 20 mg. on Day 1 and 8 mg. BID from Day 2 through Day 4)

Group 2 – 100 mg. oral netupitant plus 0.5 mg. oral palonosetron on Day 1 (with an oral dexamethasone adjusted regimen*: 12 mg. on Day 1 and 8 mg. daily from Day 2 through Day 4)

Group 3 – 200 mg. oral netupitant plus 0.5 mg. oral palonosetron on Day 1 (with an oral dexamethasone adjusted regimen*: 12 mg. on Day 1 and 8 mg. daily from Day 2 to Day 4)

Group 4 – 300 mg. oral netupitant plus 0.5 mg. oral palonosetron on Day 1 (with dexamethasone adjusted regimen*: 12 mg. on Day 1 and 8 mg. daily from Day 2 to Day 4)

Group 5 – 125 mg. oral aprepitant plus IV ondansetron 32 mg. (both on Day 1) then 80 mg. oral aprepitant on Day 2 and Day 3, (all with an oral dexamethasone adjusted regimen: 12 mg. on Day 1 and 8 mg. daily from Day 2 through Day 4)

In addition, a Group 6 was added to the analysis for comparative purposes, based on the results reported by Grunberg et al., Support Cancer Care (2009) 17:589-594:

Group 6 – 285 mg. oral aprepitant plus 20 mg. oral dexamethasone plus 0.2 mg. palonosetron i.v. (all on Day 1) then 80 mg. oral aprepitant

The primary efficacy endpoint was the complete response rate (defined as no emetic episodes, no rescue medication) within 120 hours after the start of the highly emetogenic chemotherapy administration. Secondary efficacy endpoints were:

- Complete response for the 0-24 hour interval (acute phase); and for the 25-120 hour interval (delayed phase);
- Complete protection (defined as no emesis, no rescue therapy, no significant nausea); Total control (defined as no emesis, no rescue therapy and no nausea); No nausea (maximum VAS <5 mm); No significant nausea (maximumVAS <25 mm); No rescue medication; No emesis. These endpoints were evaluated for the 0-120 hour interval (overall), acute and delayed phase.
- Time to first emetic episode, Time to first rescue medication, Time to treatment failure (based on time to the first emetic episode or time to the first rescue medication, whichever occurs first);

- Severity of nausea for the overall, acute and delayed phase; • Patient global satisfaction with anti-emetic therapy by means of VAS for each 24 hour interval.

Complete response rates are summarized in Table 5. The percent of patients with complete response over 0-120 hours after start of cisplatin administration was 76.5% in the palonosetron alone group and 87.4%, 87.6%, and 89.6% in the netupitant 100 mg., 200 mg., and 300 mg. groups, respectively. Differences from palonosetron-alone were greater than 10% (10.9% to 13.2%). All doses of netupitant were statistically superior to palonosetron alone (p-value=0.004 for the netupitant 300 mg. combination group).

TABLE 5: COMPLETE RESPONSE RATE FOR THE OVERALL, ACUTE AND DELAYED PHASE: MFAS Population

Efficacy endpoint	Palo alone (n=136)	Palo + Netu 100 mg (n=135)	Palo + Netu 200 mg (n=137)	Palo + Netu 300 mg (n=135)	Aprepitant Regimen (N=134)
CR, Overall Phase, 0-120h					
Percent of Patients	76.5	87.4	87.6	89.6	86.6
Difference from Palo alone (%)		10.9	11.1	13.2	10.1
p-value (*)		0.018	0.017	0.004	0.027
CR, Acute Phase, 0-24h					
Percent of Patients	89.7	93.3	92.7	98.5	94.8
Difference from Palo alone (%)		3.6	3.0	8.8	5.1
p-value (*)		0.278	0.383	0.007	0.114
CR, Delayed Phase, 25-120h					
Percent of Patients	80.1	90.4	91.2	90.4	88.8
Difference from Palo alone (%)		10.2	11.1	10.2	8.7
p-value (*)		0.018	0.010	0.018	0.043

(*) p-value from logistic regression analysis, aprepitant p-value from post-hoc logistic regression analysis.

Table 6 summarizes results for main secondary endpoints. In the overall phase, 76.5% of patients in the palonosetron-alone group did not experience emesis, while 87.4, 87.6, and 91.1% of patients did not experience emesis in the netupitant 100 mg., 200 mg. and 300 mg. combination groups, respectively ($p<0.05$ for all doses).

TABLE 6: SUMMARY OF SECONDARY EFFICACY
RESULTS: PERCENT OF PATIENTS, MFAS POPULATION

Efficacy endpoint	Palo alone (n=136)	Palo + Netu 100 mg (n=135)	Palo + Netu 200 mg (n=137)	Palo + Netu 300 mg (n=135)	Aprepitant Regimen (N=134)	Palo+Aprep 285 mg (N=41) **
No Emesis						
Overall	76.5	87.4*	87.6*	91.1*	87.3*	
Acute	89.7	93.3	92.7	98.5*	94.8	
Delayed	80.1	90.4*	91.2*	91.9*	89.6*	
No Rescue						
Overall	95.6	97.8	100	98.5	97.8	
Acute	97.8	99.3	100	100	100	
Delayed	97.1	97.8	100	98.5	97.8	
No Nausea						
Overall	50.7	54.8	62.0	61.5	58.2	32
Acute	75.0	72.6	77.4	80.0	77.6	59
Delayed	53.7	59.3	65.0	68.1*	60.4	41
No Significant Nausea						
Overall	79.4	80.0	86.1	89.6*	85.8	56
Acute	93.4	94.1	94.2	98.5*	94.0	79
Delayed	80.9	81.5	89.8*	90.4*	88.1	59
Total Control						
Overall	50.0	54.8	61.3	59.3	56.0	
Acute	71.3	71.9	76.6	80.0	74.6	
Delayed	52.2	59.3	65.0*	65.9*	58.2	
Complete Protection						
Overall	69.9	76.3	80.3*	83.0*	78.4	51
Acute	87.5	89.6	88.3	97.0*	89.6	76
Delayed	73.5	80.0	87.6*	84.4*	82.1	66

* p-value <0.05 compared with palonosetron-alone; aprepitant comparisons p-values calculated by post-hoc analysis
** As reported by Grunberg *et al.*, Support Cancer Care (2009) 17:589-594

EXAMPLE 7: COMPARATIVE RESULTS OF APREPITANT DOSING REGIMEN

The following Table 8 reports the results observed for an aprepitant dosing regimen, as described in the FDA approved prescribing information for aprepitant, which demonstrates, among other things, that aprepitant has no meaningful effect on nausea. Table 7 reports the dosing regimen:

TABLE 7

Treatment Regimen	Day 1	Days 2 to 4
Aprepitant	Aprepitant 125 mg PO Dexamethasone 12 mg PO Ondansetron 32 mg I.V.	Aprepitant 80 mg PO Daily (Days 2 and 3 only) Dexamethasone 8 mg PO Daily (morning)

TABLE 8

Percent of Patients Receiving Highly Emetogenic Chemotherapy Responding by Treatment Group and Phase for Study 1 — Cycle 1

ENDPOINTS	Aprepitant Regimen (N = 260)[†] %	Standard Therapy (N = 261)[†] %	p-Value
PRIMARY ENDPOINT			
Complete Response			
Overall[‡]	73	52	<0.001
OTHER PRESPECIFIED ENDPOINTS			
Complete Response			
Acute phase[§]	89	78	<0.001
Delayed phase[¶]	75	56	<0.001
Complete Protection			
Overall	63	49	0.001
Acute phase	85	75	NS*
Delayed phase	66	52	<0.001
No Emesis			
Overall	78	55	<0.001
Acute phase	90	79	0.001
Delayed phase	81	59	<0.001
No Nausea			
Overall	48	44	NS**
Delayed phase	51	48	NS**
No Significant Nausea			
Overall	73	66	NS**
Delayed phase	75	69	NS**

[†]N: Number of patients (older than 18 years of age) who received cisplatin, study drug, and had at least one post-treatment efficacy evaluation.
[‡]Overall: 0 to 120 hours post-cisplatin treatment.
[§]Acute phase: 0 to 24 hours post-cisplatin treatment.
[¶]Delayed phase: 25 to 120 hours post-cisplatin treatment.
*Not statistically significant when adjusted for multiple comparisons.

****

Throughout this application, various publications are referenced. The disclosures of these publications in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art to which this invention pertains. It will be apparent to those skilled in the art that various modifications and variations can be made in the present invention without departing from the scope or spirit of the invention. Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims.

CLAIMS

1) A method of treating nausea and vomiting for five consecutive days in a patient in need thereof, comprising:

a) administering to said patient on day one netupinant or a pharmaceutically acceptable salt thereof, in a therapeutically effective amount which is effective to treat nausea and vomiting during the acute and delayed phases of emesis, and which enters the systemic circulation, crosses the blood brain barrier and occupies at least 70% of NK_1 receptors in the striatum seventy-two hours after said administration;

b) administering to said patient on day one a therapeutically effective amount of a 5-HT_3 antagonist or a pharmaceutically acceptable salt thereof, which is effective to treat nausea and vomiting during the acute and delayed phases; and

c) administering to said patient on day one a first dose of dexamethasone which is ineffective against nausea and vomiting when administered alone, but effective against nausea and vomiting when administered in combination with said netupitant, wherein said first dose comprises from 50 to 70% of a minimum effective dose when administered alone.

2) The method of claim 1, further comprising: d) administering to said patient, on days two, three and four, a second dose of dexamethasone which is ineffective against nausea and vomiting when administered alone, but effective against nausea and vomiting when administered in combination with said netupitant, wherein said second dose comprises from 40 to 60% of a minimum effective dose when administered alone.

3) The method of claim 1 or 2, wherein said netupitant occupies at least 80% of NK_1 receptors in the striatum seventy-two hours after said administration.

4) The method of any one of claims 1 to 3, wherein only one dose of netupitant or a pharmaceutically acceptable salt thereof is administered during said five days.

5) The method of any one of claims 1 to 4, wherein only one dose of netupitant or a pharmaceutically acceptable salt thereof is administered during said five days, and said one dose is administered orally.

6) The method of any one of claims 1 to 5, wherein said therapeutically effective amount of netupitant comprises from about 200 to about 400 mg. of netupitant or a pharmaceutically acceptable salt thereof.

7) The method of any one of claims 1 to 6, wherein said therapeutically effective amount of netupitant comprises about 300 mg. of netupitant as a free base.

8) The method of any one of claims 1 to 7, wherein said therapeutically minimum effective dose of dexamethasone when administered alone comprises from about 16 mg to about 20 mg of dexamethasone.

9) The method of any one of claims 1 to 8, wherein only one dose of 5-HT_3 antagonist or a pharmaceutically acceptable salt thereof is administered during said five days.

10) The method of any one of claims 1 to 9, wherein the 5-HT_3 antagonist is ondansetron or palonosetron.

11) The method of any one of claims 1 to 10, wherein said therapeutically effective amount of 5-HT_3 antagonist comprises from about 0.25 to about 0.75 mg. of palonosetron or a pharmaceutically acceptable salt thereof.

12) The method of any one of claims 1 to 11, wherein said therapeutically effective amount of 5-HT_3 antagonist comprises about 0.56 mg. of palonosetron hydrochloride, corresponding to about 0.5 mg of palonosetron as a free base.

13) The method of any one of claims 1 to 12, wherein said palonosetron is administered orally.

14) The method of any one of claims 1 to 13, comprising orally administering:

a) about 300 mg. of netupitant as a free base on day one;

b) about 0.56 mg. of palonosetron hydrochloride, corresponding to about 0.5 mg of palonosetron as a free base, on day one; and

c) about 12 mg. of dexamethasone on day one.

15) The method of any one of claims 1 to 14, comprising orally administering:

a) about 300 mg. of netupitant as a free base on day one;

b) about 0.56 mg. of palonosetron hydrochloride (corresponding to about 0.5 mg of palonosetron as a free base) on day one;

c) about 12 mg. of dexamethasone on day one; and

d) about 8 mg. of dexamethasone on days two, three and four.

16) A method of treating nausea and vomiting for a period of five consecutive days in a patient in need thereof, comprising administering to said patient netupinant or a pharmaceutically acceptable salt thereof, in a therapeutically effective amount which is

effective to treat nausea and vomiting during the acute and delayed phases of emesis, and which enters the systemic circulation, crosses the blood brain barrier and occupies at least 70% of NK_1 receptors in the striatum seventy-two hours after said administration.

17) The method of claim 16, wherein said netupitant occupies at least 80% of NK_1 receptors in the striatum seventy-two hours after said administration

18) The method of claim 16 or 17, further comprising:

a) administering to said patient on day one a first dose of dexamethasone which is ineffective against nausea and vomiting when administered alone, but effective against nausea and vomiting when administered in combination with said netupitant, wherein said first dose comprises from 50 to 70% of a minimum effective dose when administered alone; and

b) if said patient is subject to highly emetogenic chemotherapy, administering to said patient, on days two, three and four, a second dose of dexamethasone which is ineffective against nausea and vomiting when administered alone, but effective against nausea and vomiting when administered in combination with said netupitant, wherein said second dose comprises from 40 to 60% of a minimum effective dose when administered alone.

19) The method of any one of claims 16 to 18, further comprising administering a therapeutically effective amount of a 5-HT_3 antagonist.

20) The method of any one of claims 16-19, wherein said therapeutically effective amount of netupitant comprises from about 200 to about 400 mg. of netupitant or a pharmaceutically acceptable salt thereof, said therapeutically effective amount of 5-HT_3 antagonist comprises from about 0.25 to about 0.75 mg. of palonosetron or a pharmaceutically acceptable salt thereof, and said therapeutically minimum effective dose of dexamethasone when administered alone comprises from about 16 mg to about 20 mg of dexamethasone.

21) The method of any one of claims 16-20, wherein:

a) only one dose of netupitant is administered during said five days on day one, comprising about 300 mg. of netupitant as the free base; and

b) administering about 12 mg. of dexamethasone on day one; and

c) if said patient is undergoing highly emetogenic chemotherapy, administering about 8 mg. of dexamethasone on days two, three and four.

22) The method of claim 21, further comprising administering only one dose of a 5-HT_3 antagonist during said five days on day one, comprising about 0.56 mg. of palonosetron hydrochloride, corresponding to about 0.5 mg of palonosetron as a free base.

23) The method of any one of claims 1-22, wherein said nausea and vomiting is chemotherapy induced nausea and vomiting ("CINV"), radiation therapy induced nausea and vomiting ("RINV"), or post-operative nausea and vomiting ("PONV").

24) The method of any one of claims 1-22, wherein said nausea and vomiting is induced by moderately or highly emetogenic chemotherapy.

25) The method of any one of claims 1-24, comprising administering moderately or highly emetogenic chemotherapy within from about one hour to about two hours of said administration of said netupitant or pharmaceutically acceptable salt thereof.

26) The method of any one of claims 1-25, comprising treating nausea and vomiting in response to highly emetogenic chemotherapy during the acute phase, or in response to highly emetogenic chemotherapy during the delayed phase, or in response to moderately emetogenic chemotherapy during the acute phase, or in response to moderately emetogenic chemotherapy during the delayed phase.

27) A method of treating nausea and vomiting in a human subject in need thereof, during the acute and/or delayed phases of CINV in response to moderately or highly emetogenic chemotherapy, comprising administering a therapeutically effective amount of netupitant, or a pharmaceutically acceptable salt thereof, and a therapeutically effective amount of palonosetron, or a pharmaceutically acceptable salt thereof, before said chemotherapy.

28) The method of claim 27, comprising orally administering from about 200 to about 400 mg. of netupitant or a pharmaceutically acceptable salt thereof, and from about 0.25 to about 0.75 mg. of palonosetron or a pharmaceutically acceptable salt thereof.

29) The method of claim 27 or 28, comprising orally administering about 300 mg. of netupitant as the free base, and about 0.56 mg. of palonosetron hydrochloride.

30) The method of any one of claims 27-29, further comprising, if said patient is subject to highly emetogenic chemotherapy, administering a sub-therapeutic dose of dexamethasone on days one, two, three and four.

31) The method of any one of claims 27-30, further comprising, if said patient is undergoing highly emetogenic chemotherapy, orally administering 12 mg. of dexamethasone on day one, and 8 mg. of dexamethasone on days two, three and four.

32) The method of any one of claims 1-31, wherein netupitant potentiates the therapeutic effect of dexamethasone.

33) The method of any one of claims 1-32, wherein netupitant promotes bioavailability of palonosetron.

34) An orally administered dosage form comprising a combination of palonosetron and an NK1 antagonist, or a pharmaceutically acceptable salt or prodrug thereof, comprising:

a) an outer shell;

b) one or more NK1 antagonist units housed within said outer shell, each comprising said netupitant or pharmaceutically acceptable salt or prodrug thereof and one or more pharmaceutically acceptable excipients; and

c) one or more palonosetron units housed within said outer shell, each comprising said palonosetron or pharmaceutically acceptable ester or prodrug thereof and one or more pharmaceutically acceptable excipients;

wherein said dosage form comprises (3S)-3-[(3aS)-1-oxo- 2,3,3a,4,5,6-hexahydro-1*H*-benzo[*de*] isoquinoline-2-yl]-1-azoniabicyclo[2.2.2]octan-1-olate in an amount that does not exceed 3 wt.%.

35) The dosage form of claim 34, comprising about 0.56 mg. of palonosetron hydrochloride and from about 100 to about 500 mg, or from about 200 to about 400 mg, or about 300 mg of netupitant or a pharmaceutically acceptable salt thereof.

36) The dosage form of claim 34 or 35, wherein said one or more NK1 antagonist units are in the form of one or more orally administered tablets, and said palonosetron units are in the form of one or more orally administered soft-gel capsules.

37) The dosage form of any one of claims 34 to 36, wherein each of said tablets comprises from about 50 to about 200 mg, or from about 100 to about 150 mg, or about 100 mg of netupitant.

38) The capsule of any one of claims 34 to 37, wherein said outer shell of said capsule has an oxygen permeability of less than 1.0×10^{-3} ml·cm/(cm^2·24 hr. atm).

39) The capsule of any one of claims 34 to 38, wherein each of said soft-gel capsules comprises an inner fill composition comprising from 0.1 to 2.0 mg. of palonosetron hydrochloride.

40) The capsule of any one of claims 34 to 39, wherein each of said soft-gel capsules comprises an inner fill composition comprising from 75 to 98 wt.% of one or more lipophilic components.

41) The capsule of any one of claims 34 to 40, wherein each of said soft-gel capsules comprises an outer shell having an oxygen permeability of less than 1.0×10^{-3} ml·cm/(cm^2·24 hr. atm).

42) An orally administered capsule dosage form comprising:

a) an outer shell;

b) one or more tablets housed within said outer shell, each comprising an NK1 antagonist or a pharmaceutically acceptable salt or prodrug thereof and one or more pharmaceutically acceptable excipients; and

c) one or more soft-gel capsules housed within said outer shell, each comprising palonosetron or a pharmaceutically acceptable ester or prodrug thereof and one or more pharmaceutically acceptable excipients;

wherein said dosage form comprises (3S)-3-[(3aS)-1-oxo-2,3,3a,4,5,6-hexahydro-1*H*-benzo[*de*] isoquinoline-2-yl]-1-azoniabicyclo[2.2.2]octan-1-olate in an amount that does not exceed 3 wt.%.

43) The capsule of claim 42 comprising about 0.56 mg. of palonosetron hydrochloride and from about 100 to about 500 mg, or from about 200 to about 400 mg, or about 300 mg of netupitant.

44) The capsule of claim 42 or 43, wherein said outer shell of said capsule has an oxygen permeability of less than 1.0×10^{-3} ml·cm/(cm^2·24 hr. atm).

45) The capsule of any one of claims 42 to 44, wherein each of said tablets comprises from about 50 to about 200 mg, or from about 100 to about 150 mg, or about 100 mg of netupitant or a pharmaceutically acceptable salt thereof.

46) The capsule of any one of claims 42 to 45, wherein each of said soft-gel capsules comprises an outer shell having an oxygen permeability of less than 1.0×10^{-3} ml·cm/(cm^2·24 hr. atm).

47) The capsule of any one of claims 42 to 46, wherein said soft-gel capsule comprises an inner fill composition comprising from 0.1 to 2.0 mg. of palonosetron hydrochloride.

48) The capsule of any one of claims 42 to 47, wherein said soft-gel capsule comprises an inner fill composition comprising from 75 to 98 wt.% of one or more lipophilic components.

49) The dosage form or capsule of any one of claims 34 to 48, wherein netupitant and palonosetron are formulated in separate form and then combined in one dosage.

50) A method of treating emesis comprising administering to a human in need thereof the dosage form of any one of claims 34-51.

51) The method of claim 50 wherein said emesis is delayed-onset emesis.

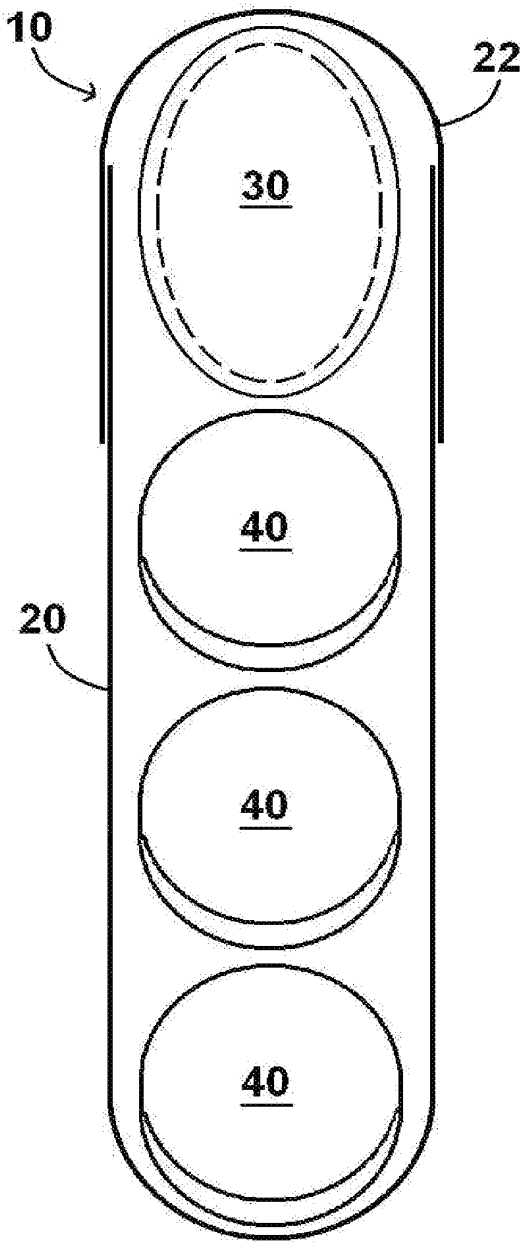


Figure 1

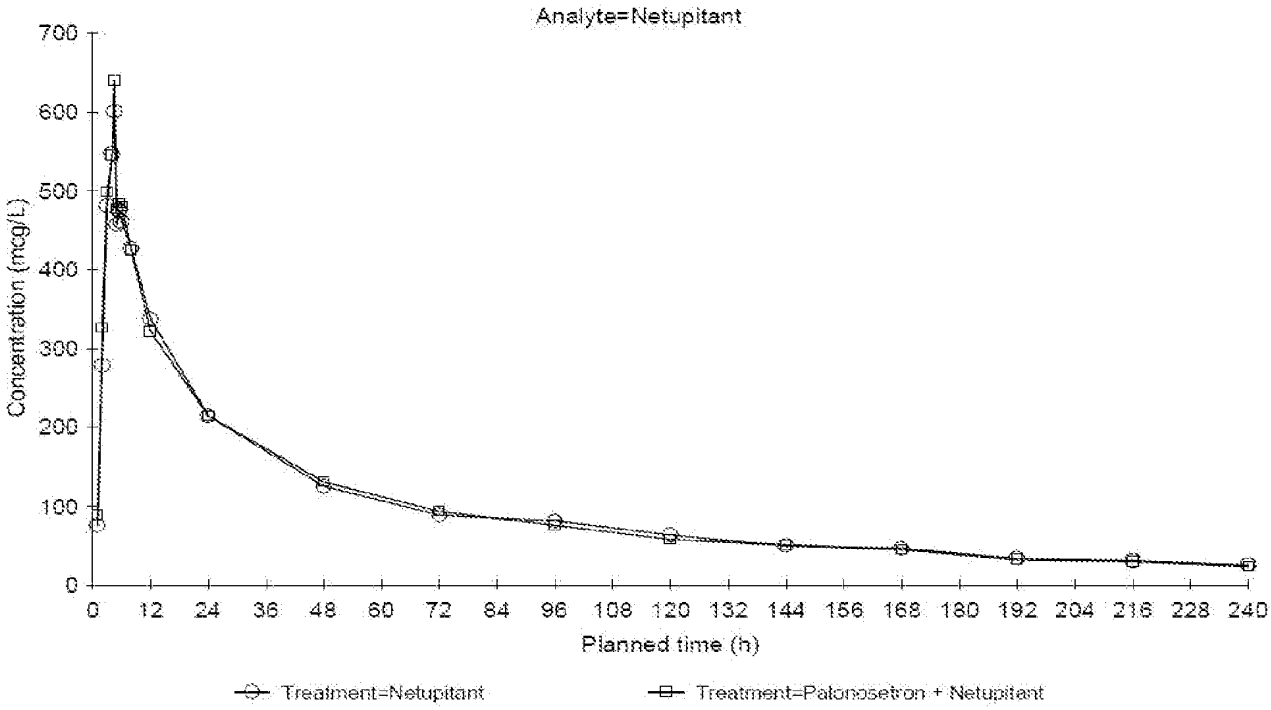

Analyte=Netupitant
Concentration (mcg/L)
700
600
500
400
300
200
100
0
0 12 24 36 48 60 72 84 96 108 120 132 144 156 168 180 192 204 216 228 240
Planned time (h)
Treatment=Netupitant
Treatment=Palonosetron + Netupitant

Figure 2

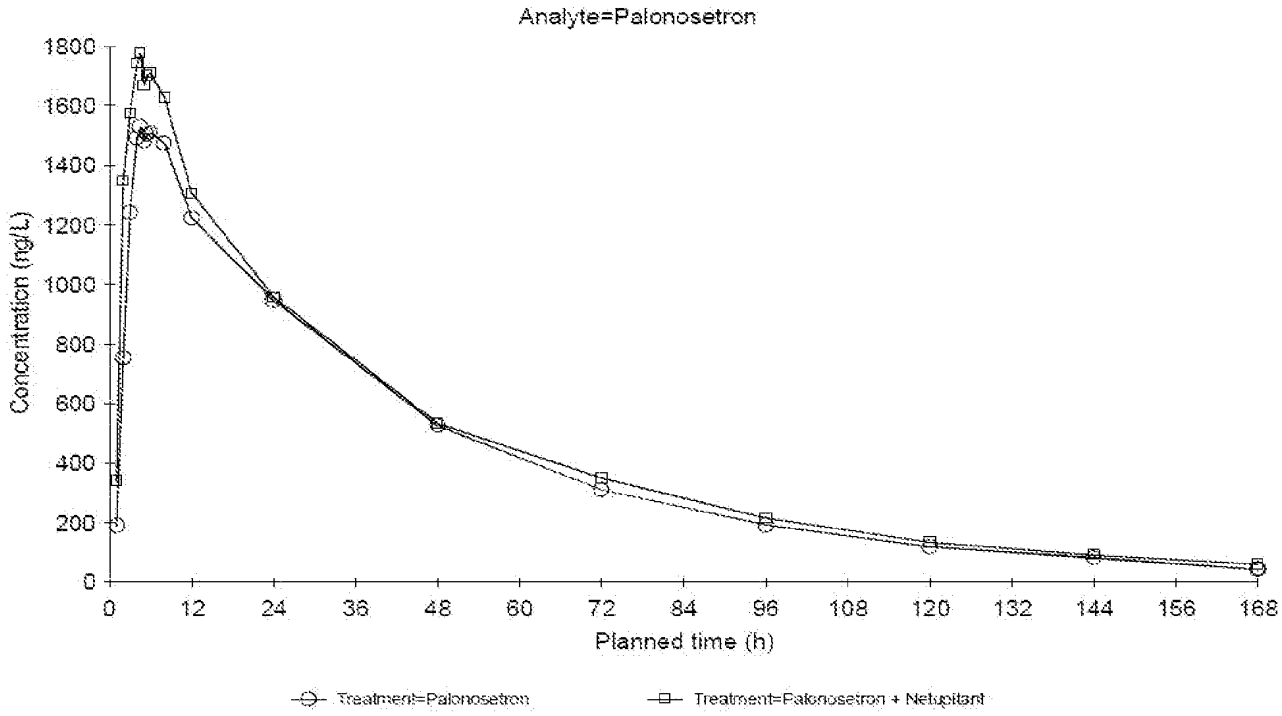

Analyte=Palonosetron
Concentration (ng/L)
1800
1600
1400
1200
1000
800
600
400
200
0
0
12
24
36
48
60
72
84
96
108
120
132
144
156
168
Planned time (h)
Treatment=Palonosetron
Treatment=Palonosetron + Netupitant

Figure 3

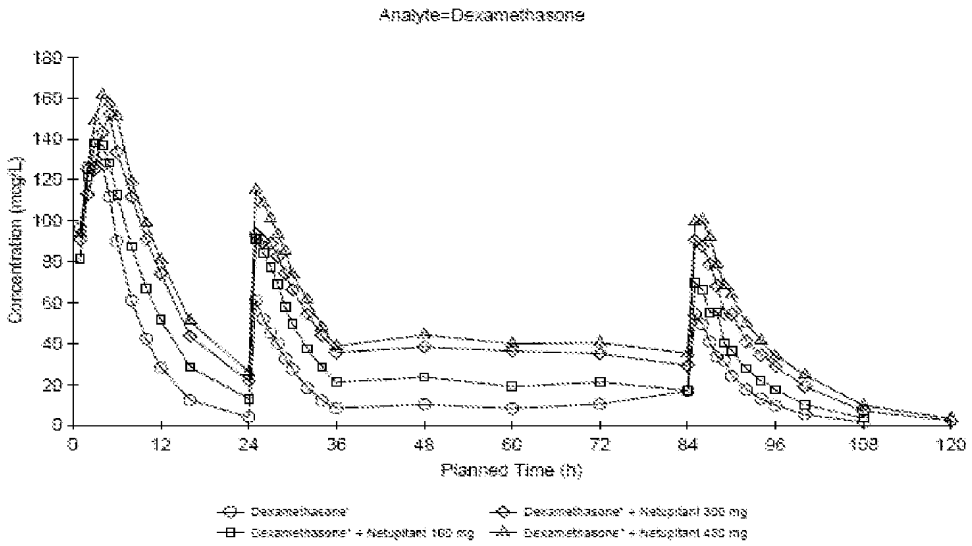


Figure 4: Dexamethasone Mean Plasma Concentrations Versus Time, With and Without Co-administration of Netupitant.

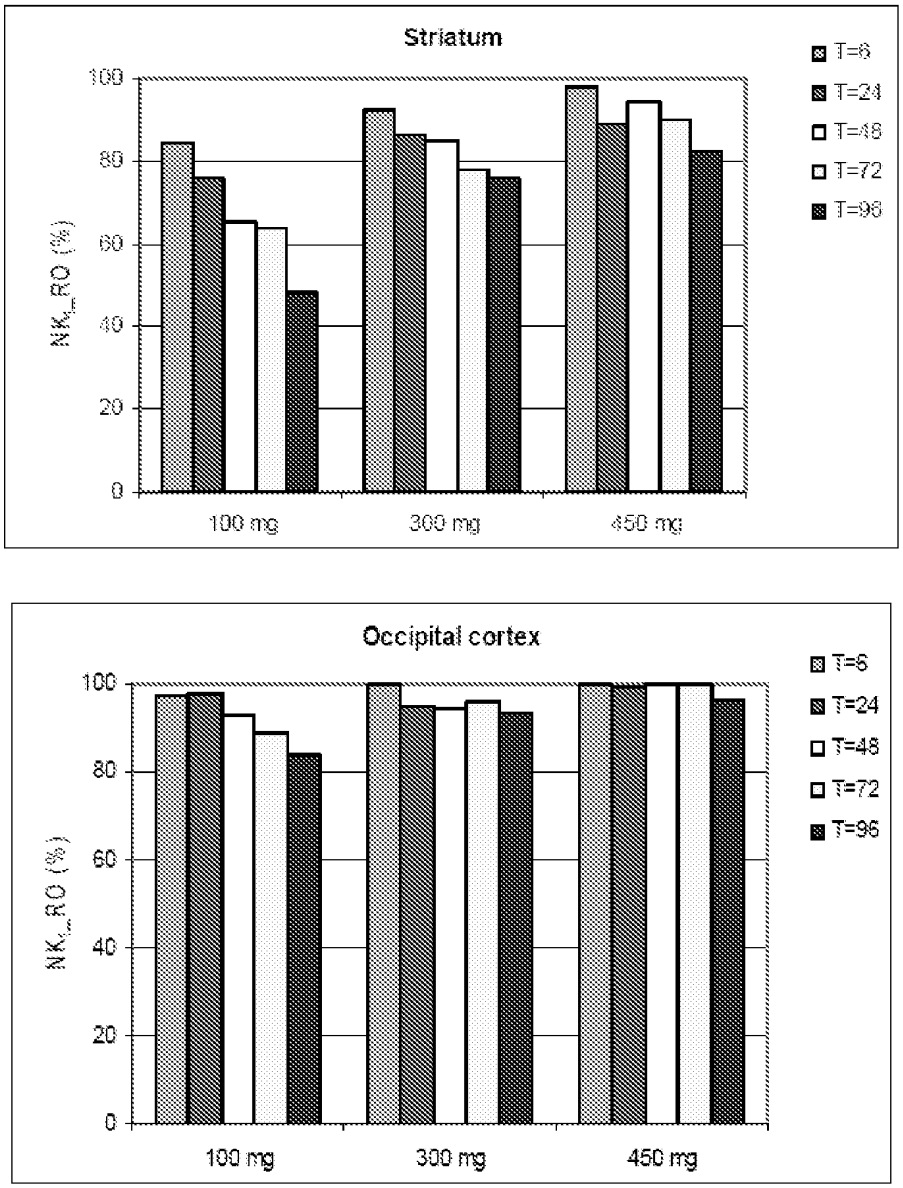


Figure 5: Average Neurokinin 1 Receptor Occupancy (NK_1-RO), Obtained at 6, 24, 48, 72 and 96 Hours after a Single Oral Dose of 100, 300 and 450 mg. netupitant (N=2 for each dose) in Striatum and Occipital Cortex, PET Study

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2010/003106

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/4178 A61K31/473 A61K31/496 A61K31/573 A61K45/06
A61P1/08
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 A61P

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 practical, search terms used)
EPO-Internal, WPI Data, EMBASE, BIOSIS, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	REDDY G KESAVA ET AL: "Novel neurokinin-1 antagonists as antiemetics for the treatment of chemotherapy-induced emesis.", SUPPORTIVE CANCER THERAPY 1 APR 2006 LNKD-PUBMED:18632487, vol. 3, no. 3, 1 April 2006 (2006-04-01), pages 140-142, XP002626039, ISSN: 1543-2912	16,17, 23,24
Y	* abstract page 141; table 1	1-15, 18-22, 25-51
	----- -/--	

[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 document 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
4 March 2011	14/03/2011

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	Opravz, Petra

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.
Y	DIEMUNSCH P ET AL: "Neurokinin-1 receptor antagonists in the prevention of postoperative nausea and vomiting.", BRITISH JOURNAL OF ANAESTHESIA JUL 2009 LNKD- PUBMED:19454547, vol. 103, no. 1, July 2009 (2009-07), pages 7-13, XP002626040, ISSN: 1471-6771 page 10, left-hand column	1-10,19, 32
Y	WO 2008/049552 A1 (HELSINN HEALTHCARE SA [CH]; BONADEO DANIELE [IT]; CALDERARI GIORGIO [C) 2 May 2008 (2008-05-02) page 11 page 16, line 20 - line 27	11-15, 18, 20-22, 25-31, 33-51
Y	DE WIT R: "Current position of 5HT3 antagonists and the additional value of NK1 antagonists; a new class of antiemetics.", BRITISH JOURNAL OF CANCER 16 JUN 2003 LNKD- PUBMED:12799621, vol. 88, no. 12, 16 June 2003 (2003-06-16) , pages 1823-1827, XP002626041, ISSN: 0007-0920 * abstract	11-15, 18, 20-22, 25-31, 33-51
Y	GRUNBERG STEVEN M 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.", SUPPORTIVE CARE IN CANCER : OFFICIAL JOURNAL OF THE MULTINATIONAL ASSOCIATION OF SUPPORTIVE CARE IN CANCER MAY 2009 LNKD- PUBMED:19037667, vol. 17, no. 5, May 2009 (2009-05), pages 589-594, XP002626042, ISSN: 1433-7339 page 590, paragraph 4th	11-15, 18, 20-22, 25-31, 33-51
A	DIEMUNSCH PIERRE ET AL: "Potential of substance P antagonists as antiemetics", 1 January 2003 (2003-01-01), ANTIEMETIC THERAPY, BASEL [U.A.] : KARGER, CH, PAGE(S) 78 - 97, XP008133831, ISBN: 978-3-8055-7547-8 the whole document	1-51

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2010/003106

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2008049552 A1	02-05-2008	AR 063362 A1	21-01-2009
		AT 427742 T	15-04-2009
		AU 2007308378 A1	02-05-2008
		CA 2666512 A1	02-05-2008
		CL 30552007 A1	24-03-2008
		CN 101573106 A	04-11-2009
		CR 10728 A	23-07-2009
		DK 1940366 T3	29-06-2009
		EA 200970396 A1	30-10-2009
		EP 1940366 A1	09-07-2008
		ES 2325339 T3	01-09-2009
		HK 1117769 A1	14-08-2009
		HR 20090341 T1	31-07-2009
		JP 2009507933 T	26-02-2009
		KR 20090073234 A	02-07-2009
		PT 1940366 E	17-06-2009
		SI 1940366 T1	31-08-2009
		SV 2009003238 A	09-11-2009
		US 2008152704 A1	26-06-2008
		ZA 200902773 A	31-03-2010

Docket No.: HHC002US6
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Trento et al.	)	Customer No.: 140619
Application No.: 15/003,327	)	Confirmation No.: 1097
Filing Date: 01-21-2016	)	Art Unit: 1612
For: COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING	)	Examiner: WEBB, WALTER E.

INFORMATION DISCLOSURE STATEMENT

Commissioner for Patents
Alexandria, VA 22313-1450

Dear Madam:

Filed currently herewith is a form SB08 in compliance with 37 C.F.R. §§ 1.56, 1.97 and 1.98. In accordance with section 1.98(a)(2)(ii), copies of published U.S. patents and U.S. patent publications are omitted. In accordance with section 1.98(d), copies of foreign patent documents and non-patent literature are omitted to the extent they were previously provided in U.S.S.N. 14/069,970 and 13/077,462, to which this application claims priority.

This submission does not represent that a search has been made or that no better art exists and does not constitute an admission that each or all of the listed documents are material or constitute "prior art." If the Examiner applies any of the documents as prior art against any claim in the application and Applicant determines that the cited documents do not constitute "prior art" under United States law, Applicant reserves the right to present to the U.S. Patent and Trademark Office the relevant facts and law regarding the appropriate status of such documents.

If there is any fee due in connection with the filing of this statement, please charge the fee to Deposit Account No. 600254.

Respectfully submitted,

By: /Clark G. Sullivan/
Clark G. Sullivan
Reg. No. 36,942

September 15, 2016
Customer No. 140619
Attorney Docket No.: HHC002.US6

Electronic Patent Application Fee Transmittal

Application Number:	15003327
Filing Date:	21-Jan-2016
Title of Invention:	COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING
First Named Inventor/Applicant Name:	Fabio TRENTO
Filer:	Clark G. Sullivan
Attorney Docket Number:	HHC002

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
		Total in USD ($)		**180**

Electronic Acknowledgement Receipt

EFS ID:	26930480
Application Number:	15003327
International Application Number:	
Confirmation Number:	1097
Title of Invention:	COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING
First Named Inventor/Applicant Name:	Fabio TRENTO
Customer Number:	140619
Filer:	Clark G. Sullivan
Filer Authorized By:	
Attorney Docket Number:	HHC002
Receipt Date:	15-SEP-2016
Filing Date:	21-JAN-2016
Time Stamp:	18:31:46
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$180
RAM confirmation Number	091616INTEFSW18322800
Deposit Account	1009
Authorized User	Clark Sullivan

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Information Disclosure Statement (IDS) Form (SB08)	HHC002_IDS_1449.pdf	614090 3eb24d54d013f4d3249afab60b632243b6df8625	no	5
Warnings:					
Information:					
A U.S. Patent Number Citation or a U.S. Publication Number Citation is required in the Information Disclosure Statement (IDS) form for autoloading of data into USPTO systems. You may remove the form to add the required data in order to correct the Informational Message if you are citing U.S. References. If you chose not to include U.S. References, the image of the form will be processed and be made available within the Image File Wrapper (IFW) system. However, no data will be extracted from this form. Any additional data such as Foreign Patent Documents or Non Patent Literature will be manually reviewed and keyed into USPTO systems.					
2	Foreign Reference	WO2011061622.pdf	2050210 2f33ca5c3eecc68a938416c26d6fd47148895ac4	no	43
Warnings:					
Information:					
3	Transmittal Letter	HHC002_IDS_Transmittal.pdf	83200 642611865e3fd0f397c18e3d58e923b5bb2641dd	no	2
Warnings:					
Information:					
4	Fee Worksheet (SB06)	fee-info.pdf	30544 32bec8d899edfdb26ae6de6907274a0b539e1b17	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	2778044		

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 a 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.

Docket No.: HHC002US6/CO001
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Trento et al.	)	Customer No.: 140619
Application No.: 15/003,327	)	Confirmation No.: 1097
Filing Date: 01-21-2016	)	Art Unit: 1612
For: COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING	)	Examiner: WEBB, WALTER E.

AMENDMENT AFTER FINAL

Commissioner for Patents
Alexandria, VA 22313-1450

Dear Sir:

In response to the Final Rejection notified in the above-referenced application on September 1, 2016, please enter the following amendments and consider the following remarks.

A REPLACEMENT CLAIM SET begins on page 2.

REMARKS begin on page 6.

REPLACEMENT CLAIM SET

1)-15) (CANCELED)

16) (CURRENTLY AMENDED) A method of treating nausea and vomiting from an emesis-inducing event for a period of five consecutive days in a patient in need thereof, comprising administering to said patient netupitant or a pharmaceutically acceptable salt thereof, in a therapeutically effective amount which is effective to treat nausea and vomiting during the acute and delayed phases of emesis, and which enters the systemic circulation, crosses the blood brain barrier and occupies 70% or more of NK_1 receptors in the striatum seventy-two hours after said administration, wherein said therapeutically effective dose ~~comprises~~ consists of a single dose of netupitant or pharmaceutically acceptable salt thereof administered on day one of said five consecutive days.

17) (PREVIOUSLY PRESENTED) The method of claim 16, wherein said netupitant occupies 80% or more of NK_1 receptors in the striatum seventy-two hours after said administration.

18) (PREVIOUSLY PRESENTED) The method of claim 16, further comprising: a) administering to said patient on day one a first dose of dexamethasone which is ineffective against nausea and vomiting when administered alone, but effective against nausea and vomiting when administered in combination with said netupitant, wherein said first dose comprises from 50 to 70% of a minimum effective dose when administered alone; and b) if said patient is subject to highly emetogenic chemotherapy, administering to said patient, on days two, three and four, a second dose of dexamethasone which is ineffective against nausea and vomiting when administered alone, but effective against nausea and vomiting when administered in combination with said netupitant, wherein said second dose comprises from 40 to 60% of a minimum effective dose when administered alone.

19) (CANCELED)

20) (CANCELED)

21) (PREVIOUSLY PRESENTED) The method of claim 16 wherein: a) only one dose of netupitant is administered during said five days on day one, comprising about 300 mg. of netupitant as the free base; and b) administering about 12 mg. of dexamethasone on day

one; and c) if said patient is undergoing highly emetogenic chemotherapy, administering about 8 mg. of dexamethasone on days two, three and four.

22) (CANCELED)

23) (PREVIOUSLY PRESENTED) The method of claim 16 wherein said nausea and vomiting is chemotherapy induced nausea and vomiting ("CINV"), radiation therapy induced nausea and vomiting ("RINV"), or post-operative nausea and vomiting ("PONV").

24) (PREVIOUSLY PRESENTED) The method of claim 16 wherein said nausea and vomiting is induced by moderately or highly emetogenic chemotherapy.

25) (PREVIOUSLY PRESENTED) The method of claim 16 comprising administering moderately or highly emetogenic chemotherapy within from about one hour to about two hours of said administration of said netupitant or pharmaceutically acceptable salt thereof.

26) (PREVIOUSLY PRESENTED) The method of claim 16 comprising treating nausea and vomiting in response to highly emetogenic chemotherapy during the acute phase, or in response to highly emetogenic chemotherapy during the delayed phase, or in response to moderately emetogenic chemotherapy during the acute phase, or in response to moderately emetogenic chemotherapy during the delayed phase.

27) -51) (CANCELED)

52) (PREVIOUSLY PRESENTED) The method of claim 16, comprising orally administering from about 200 to about 400 mg of netupitant as the free base.

53) (PREVIOUSLY PRESENTED) The method of claim 16, comprising orally administering about 300 mg of netupitant as the free base.

54) (CURRENTLY AMENDED) A method of treating nausea and vomiting in response to an emesis-inducing event for a period of five consecutive days in a patient in need thereof, comprising administering to said patient netupitant or a pharmaceutically acceptable salt thereof, in a therapeutically effective amount which is effective to treat nausea and vomiting during the acute and delayed phases of emesis, wherein said therapeutically effective amount of netupitant or pharmaceutically acceptable salt thereof is administered on day one of said five consecutive days <u>without further administration of netupitant or a pharmaceutically acceptable salt thereof during said five consecutive days</u>.

55) (PREVIOUSLY PRESENTED) The method of claim 54, comprising orally administering from about 200 to about 400 mg of netupitant as the free base.

56) (PREVIOUSLY PRESENTED) The method of claim 54, comprising orally administering about 300 mg of netupitant as the free base.

57) (NEW) A method of treating chemotherapy induced nausea and vomiting (CINV) for five consecutive days comprising inducing in a subject receiving chemotherapy blood levels of netupitant effective to treat said CINV prior to administration of chemotherapy in said subject, without administering netupitant or a pharmaceutically acceptable salt thereof after said inducing during said five consecutive days.

58) (NEW) The method of claim 57, wherein when said chemotherapy is highly emetic chemotherapy, the chemotherapy is selected from the group consisting of carmustine, cisplatin, cyclophosphamide $\geq$ 1500 mg/m^2, dacarbazine, dactinomycin, mechlorethamine, streptozotocin and combinations thereof.

59) (NEW) The method of claim 57, wherein when said chemotherapy is moderately emetic chemotherapy, the chemotherapy is selected from the group consisting of carboplatin, cyclophosphamide < 1500 mg/m^2, cytarabine > 1 mg/m^2, daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, oxaliplatin and combinations thereof.

60) (NEW) The method of claim 57, wherein said chemotherapy is selected from the group consisting of carboplatin, cyclophosphamide, cytarabine > 1 mg/m^2, daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, carmustine, cisplatin, dacarbazine, dactinomycin, mechlorethamine, streptozotocin, oxaliplatin and combinations thereof.

61) (NEW) The method of claim 57, wherein said treatment of CINV is defined as no emetic episodes and no use of rescue medication following said chemotherapy.

62) (NEW) The method of claim 57, wherein: a) said blood levels are induced by an intravenous anti-emetic regimen administered prior to said chemotherapy; and b) said regimen is effective to treat said CINV for a five-day period after said chemotherapy.

63) (NEW) The method of claim 57, wherein: a) said treatment of CINV is defined as no emetic episodes and no use of rescue medication following said chemotherapy b) said blood levels

are induced by an intravenous anti-emetic regimen administered prior to said chemotherapy; and c) said regimen is effective to treat said CINV for a five-day period after said chemotherapy.

64) (NEW) The method of claim 63, wherein said netupitant occupies at least 70% of said patient's striatum NK1 receptors ninety-six hours after said administration.

65) (NEW) The method of claim 63, wherein said chemotherapy is highly emetogenic chemotherapy, said netupitant blood levels are effective to treat said CINV during the acute and delayed phases of said CINV, and said palonosetron blood levels are effective to treat said CINV during the acute phase of said CINV.

66) (NEW) The method of claim 63, wherein said chemotherapy is moderately emetogenic chemotherapy, said netupitant blood levels are effective to treat said CINV during the acute and delayed phases of said CINV, and said palonosetron blood levels are effective to treat said CINV during the acute phase of said CINV.

67) (NEW) The method of claim 63, wherein said chemotherapy is highly emetogenic chemotherapy, and said regimen is effective to prevent or reduce the severity of nausea during the acute and delayed phases.

68) (NEW) The method of claim 63, wherein said chemotherapy is moderately emetogenic chemotherapy, and said regimen is effective to prevent or reduce the severity of nausea during the acute and delayed phases.

69) (NEW) The method of claim 63, wherein said chemotherapy comprises cisplatin.

70) (NEW) The method of claim 63, wherein said chemotherapy comprises carboplatin, cisplatin, oxaliplatin, or doxorubicin.

71) (NEW) The method of claim 63, wherein said chemotherapy comprises cyclophosphamide.

REMARKS

Status of Claims

After the amendment, claims 16-18, 21, 23-26, and 52-71 are pending. Claims 16 and 54 are amended to further clarify that only one dose of netupitant is administered during the five-day period of acute and delayed emesis. Claims 57-71 are added based generally on claims 4 *et seq.* from U.S. Patent No. 9,186,357, but omitting the requirement for palonosetron administration. No new matter is added by the amendment.

Claim Rejections – 35 U.S.C. § 103

The Examiner continues to reject the pending claims as allegedly obvious over Reddy, a general review article summarizing the major points from the 4th Annual Future of Supportive Therapy in Oncology conference in Dallas Texas on February 24-26, 2006. Reddy discusses several developments in anti-emetics, and several NK1 antagonists either approved or under development to supplement 5HT3 and dexamethasone anti-emetic therapies. Reddy presents a very high level overview of these NK1 antagonists, without explaining the scientific rationale behind the use of NK1 antagonists, or the dosing regimen to be used for the NK1 antagonist.

For example, Reddy does not mention that NK1 antagonists were developed primarily to treat emesis occurring during the delayed phase because most 5HT3 antagonists are ineffective during the delayed phase. Clinical research has shown, for the most part, that 5HT3 antagonists are unable to prevent emesis that occurs during the delayed phase. For example, in 2005, Geling reported 10 separate clinical trials in which 5HT3 antagonists were administered during the delayed phase to treat delayed emesis. In 9 of these studies, the 5HT3 antagonist failed to statistically significantly reduce emesis during the delayed phase. A copy of Geling (2005) is provided as NPL reference 2 in the information disclosure statement filed concurrently herewith.

Reddy also does not mention that acute phase emesis generally is mediated through the 5HT3 pathway, while delayed phase emesis generally is mediated through the NK1 pathway. NK1 antagonists and 5HT3 antagonists complement each other, with the 5HT3 antagonist acting first during the acute phase, and the NK1 antagonist acting subsequently during the delayed phase.

Hesketh explained this concept of mutual complementation in an article he published in 2003, stating:

> The difference in the time course of emesis blockade observed with two different classes of receptor antagonists provides substantial evidence for involvement of separate pathophysiological mechanisms in chemotherapy-induced vomiting. Serotonin mediates the early vomiting process that occurs within 8–12 h following cisplatin-based chemotherapy, after which time substance P acting at NK1 receptors becomes the dominant mediator of vomiting.

See Hesketh (2003) abstract, NPL reference 1 in information disclosure statement filed concurrently herewith.

Finally, Reddy does not mention any dosing regimens for NK1 antagonists. When the current invention was made, clinicians used a variety of dosing regimens to prevent emesis during the delayed phase. Geling (2005), for example, reports that clinicians would administer 5HT3 antagonists several times during the delayed phase. It was also standard of care to administer a corticosteroid such as dexamethasone during the delayed phase, in addition to the 5HT3 antagonist. See, e.g., the 1998 Guidelines from the Multinational Association of Supportive Care in Cancer (MASCC) (NPL reference 3 in information disclosure statement filed concurrently herewith) (recommending in Table 2 administration of dexamethasone plus metoclopramide or 5HT3 antagonist during delayed phase, referring to studies in which the dexamethasone was administered on all four days of the delayed emesis period). In addition, when this application was filed, FDA had approved only one other NK antagonist, aprepitant, and the manufacturer (Merck) recommend that this drug be administered three times, once before chemotherapy was initiated, and two additional times on days two and three, to prevent emesis during the delayed phase. See FDA-approved prescribing information for aprepitant cited as NPL reference 4 in information disclosure statement filed concurrently herewith.

These references all suggested that the anti-emetic should be administered during the delayed phase to treat delayed phase emesis, whether the antiemetic was a 5HT3 antagonist, a corticosteroid such as dexamethasone, or an NK1 antagonist.

Once this background is considered, it becomes abundantly clear that Reddy did not teach or suggest the use of a single dose of netupitant to treat emesis for five consecutive days, without administering a second dose during the five-day period. It also becomes clear that the ability of netupitant to treat emesis during the acute phase is both surprising and unexpected.

Reddy does not support a prima facie case of obviousness because it fails to explain why a worker of ordinary skill would have administered only one dose of netupitant over a five day period.

In support of his prima facie case of obviousness the Examiner cited Reddy, and takes the position that it would have been obvious to administer only one dose of netupitant over a five-day period following CINV because of the familiarity of working with NK1 antagonists such as aprepitant. As stated by the Examiner on page 6 of the Office Action:

> Thus, it would have been obvious to administer netupitant on day one of five consecutive days. The familiarity of working with an NK-1 antagonist and its intended use make obvious the administration of netupitant, as claimed, based on the administration of other NK-1 antagonists, e.g. aprepitant.

This argument overlooks the fact that aprepitant is administered three times during the 5-day emetic period following chemotherapy. See FDA Prescribing Information for Aprepitant (NPL reference 4 in information disclosure statement cited concurrently herewith). Someone following aprepitant's teachings, as suggested by the Examiner, would administer netupitant three times during the 5-day emetic period, not one time as recited in the pending claims, before chemotherapy is even administered.

As noted above, the prior art generally taught that it was necessary to administer anti-emetic medications during the delayed phase to prevent emesis. Geling (2005) described 10 clinical trials in which 5HT3 antagonists were administered during the delayed phase. The MASCC Guidelines recommended administration of dexamethasone multiple times during the delayed phase, and FDA's approved labeling for aprepitant instructed doctors to administer aprepitant twice during the delayed phase. These references overwhelmingly taught the need to administer an antiemetic during the delayed phase when trying to prevent emesis during the delayed phase.

Reddy does not contradict these teachings or say anything to suggest that netupitant did not need to be administered during the delayed phase to prevent CINV. In the absence of any such teachings, Reddy does not support a prima facie case of obviousness.

Netupitant's efficacy during the acute phase is unexpected and further proves the patentability of the claimed invention.

As shown in Table 5 of the instant specification, netupitant is able to treat emesis in the acute phase, but aprepitant is not, when compared to a standard dosing regimen of palonosetron and dexamethasone. The Examiner, however, refuses to acknowledge the significance of this result, believing that one would expect netupitant to be effective during the acute phase. The Examiner states in his office action that:

> the Examiner was unable to confirm in the disclosure that treatment during the acute phase was unexpected. As the Examiner understands, chemotherapy-induced nausea and vomiting can be broadly categorized as acute or delayed and it is important to treat during the acute phase (within 24 hrs.) to control the delayed emesis. Therefore, artisan would have reasonably been expected to treat emesis during the acute phase.

In essence, the Examiner believes that NK1 antagonists are effective during the delayed phase because they control emesis during the acute phase.

However, as discussed above, the Examiner's rationale is not supported by Reddy, and it is inconsistent with teachings in Hesketh (2003) (NPL reference 1 in the Information Disclosure Statement filed concurrently herewith). As Hesketh (2003) explains, "Serotonin [the natural ligand for 5HT3 receptors] mediates the early vomiting process that occurs within 8–12 h following cisplatin-based chemotherapy, after which time substance P acting at NK1 receptors becomes the dominant mediator of vomiting." If, as Hesketh explains, the 5HT3 pathway mediates emesis during the acute phase, and the NK1 pathway is only implicated in the delayed phase, a worker of ordinary skill would not expect netupitant to be effective during the acute phase.

The ability of netupitant to treat emesis during the acute phase, when aprepitant was not, as reported in Table 5, was unexpected, and further proves the patentability of the current invention.

Non-statutory obviousness type double patenting

The Office Action also rejects the pending claims based on non-statutory obviousness-type double patenting over various previously granted patents in the same family as this one:

- U.S. 8,623,826
- U.S. 9,186,357
- U.S. 9,271,975

While Applicant respectfully disagrees with the rejection, Applicant is filing a suitable terminal disclaimer herewith out of a spirit of cooperation in order to have this application more promptly allowed. Applicant is also filing a terminal disclaimer over U.S. 8,951,969 for the sake of good order.

CONCLUSION

If there is any fee due in connection with this filing, please charge the fee to Deposit Account No. 600254.

Respectfully submitted,

Sullivan IP Solutions, LLC
PO Box 2252
New York NY 10163
404.483.9360

Customer No. 140619

By: /Clark G. Sullivan/
Clark G. Sullivan
Reg. No. 36,942

Electronic Patent Application Fee Transmittal

Application Number:	15003327
Filing Date:	21-Jan-2016
Title of Invention:	COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING
First Named Inventor/Applicant Name:	Fabio TRENTO
Filer:	Clark G. Sullivan
Attorney Docket Number:	HHC002US6/CO001

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
		Total in USD ($)		**180**

Electronic Acknowledgement Receipt

EFS ID:	27639324
Application Number:	15003327
International Application Number:	
Confirmation Number:	1097
Title of Invention:	COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING
First Named Inventor/Applicant Name:	Fabio TRENTO
Customer Number:	140619
Filer:	Clark G. Sullivan
Filer Authorized By:	
Attorney Docket Number:	HHC002US6/CO001
Receipt Date:	29-NOV-2016
Filing Date:	21-JAN-2016
Time Stamp:	16:00:35
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$180
RAM confirmation Number	113016INTEFSW16011300
Deposit Account	
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Non Patent Literature	Emend.pdf	628178 90800f02ecfd79e601c56e628cb3023358ab062c	no	32
Warnings:					
Information:					
2	Non Patent Literature	Geling_2005.pdf	109153 1297821a705bc5191372ed851ec9fab95d88a21e	no	6
Warnings:					
Information:					
3	Non Patent Literature	Hesketh.pdf	260805 3a04044af7c7882b401c1be63643fb93b5c25b9a	no	7
Warnings:					
Information:					
4	Information Disclosure Statement (IDS) Form (SB08)	HHC002_IDS_1449.pdf	612458 53e8bc5e02d98f7fa05949a9dfc9af4857b16b47	no	4
Warnings:					
Information:					
A U.S. Patent Number Citation or a U.S. Publication Number Citation is required in the Information Disclosure Statement (IDS) form for autoloading of data into USPTO systems. You may remove the form to add the required data in order to correct the Informational Message if you are citing U.S. References. If you chose not to include U.S. References, the image of the form will be processed and be made available within the Image File Wrapper (IFW) system. However, no data will be extracted from this form. Any additional data such as Foreign Patent Documents or Non Patent Literature will be manually reviewed and keyed into USPTO systems.					
5	Non Patent Literature	MASCC.pdf	2109234 a7ef89aba5dbe533467cfbf909727a39724af176	no	10
Warnings:					
Information:					

6	Transmittal Letter	HHC002_IDS_Transmittal.pdf	52024 e0e9530906857ac4a524b843c4b565790bac2e99	no	2
Warnings:					
Information:					
7		US_11_2016_Amendment_AF.pdf	119013 0465e5afede0170d5cafd50ab3877b713b26561f	yes	10

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Response After Final Action	1	1
	Claims	2	5
	Applicant Arguments/Remarks Made in an Amendment	6	10

Warnings:					
Information:					
8	Fee Worksheet (SB06)	fee-info.pdf	30577 26c61290a917cc91bfaa1a001cba43d2c3a91fcc	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	3921442		

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 a 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.

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
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.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	15003327
Filing Date	2016-01-21
First Named Inventor	TRENTO et al.
Art Unit	1612
Examiner Name	Walter E. Webb
Attorney Docket Number	HHC002

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Patent citation information please click the Add button. Add

U.S.PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Published Application citation information please click the Add button. Add

FOREIGN PATENT DOCUMENTS Remove

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1							

If you wish to add additional Foreign Patent Document citation information please click the Add button Add

NON-PATENT LITERATURE DOCUMENTS Remove

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, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	15003327
	Filing Date	2016-01-21
	First Named Inventor	TRENTO et al.
	Art Unit	1612
	Examiner Name	Walter E. Webb
	Attorney Docket Number	HHC002

	1	Emend Capsules and Emend for Oral Suspension: Prescribing information; 2003-2015 Merck Sharp & Dohme Corp. (Merck & Co., Inc.)
	2	Geling et al. Should 5-Hydroxytryptamine-3 Receptor Antagonists Be Administered Beyond 24 Hours After Chemotherapy to Prevent Delayed Emesis? Systematic Re-Evaluation of Clinical Evidence and Drug Cost Implications ; Journal of Clinical Oncology; Vol. 23(6) February 20, 2005; pp. 1289 - 1294.
	3	Hesketh et al. Differential involvement of neurotransmitters through the time course of cisplatin-induced emesis as revealed by therapy with specific receptor antagonists; European Journal of Cancer 39 (2003) 1074–1080.
	4	Prevention of chemotherapy- and radiotherapy-induced emesis: Results of the Perugia Consensus Conference; MASCC; Annals of Oncology 9: 811-819, 1998

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

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

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	15003327
	Filing Date	2016-01-21
	First Named Inventor	TRENTO et al.
	Art Unit	1612
	Examiner Name	Walter E. Webb
	Attorney Docket Number	HHC002

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Clark G. Sullivan/	Date (YYYY-MM-DD)	2016-11-29
Name/Print	Clark G. Sullivan	Registration Number	36942

This collection of information is required by 37 CFR 1.97 and 1.98. 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 1 hour 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.**

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. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

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.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Docket No.: HHC002US6
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Trento et al.	)	Customer No.: 140619
Application No.: 15/003,327	)	Confirmation No.: 1097
Filing Date: 01-21-2016	)	Art Unit: 1612
For: COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING	)	Examiner: WEBB, WALTER E.

INFORMATION DISCLOSURE STATEMENT

Commissioner for Patents
Alexandria, VA 22313-1450

Dear Sir:

Filed currently herewith is a form SB08 in compliance with 37 C.F.R. §§ 1.56, 1.97 and 1.98. The SB08 cites four NPL references, which are being filed concurrently herewith.

This submission does not represent that a search has been made or that no better art exists and does not constitute an admission that each or all the listed documents are material or constitute "prior art." If the Examiner applies any of the documents as prior art against any claim in the application and Applicant determines that the cited documents do not constitute "prior art" under United States law, Applicant reserves the right to present to the U.S. Patent and Trademark Office the relevant facts and law regarding the appropriate status of such documents.

The fee of $180 is being paid herewith. However, if there is any fee due in connection with the filing of this statement, please charge the fee to Deposit Account No. 600254.

Respectfully submitted,

By: /Clark G. Sullivan/
Clark G. Sullivan
Reg. No. 36,942

November 29, 2016
Customer No. 140619
Attorney Docket No.: HHC002US6

Document code: WFEE

United States Patent and Trademark Office
Sales Receipt for Accounting Date: 12/05/2016

YCHADWIC SALE #00000001 Mailroom Dt: 11/29/2016 600254 15003327
01 FC : 1202 640.00 DA

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. 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 displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 15/003,327	Filing Date 01/21/2016	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ 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).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT **11/29/2016**

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 28	Minus	** 20	= 8	X $80 =	640
Independent (37 CFR 1.16(h))	* 3	Minus	***3	= 0	X $420 =	0
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	**640**

AMENDMENT

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					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 number found in the appropriate box in column 1.

LIE
YOLANDA CHADWICK

This collection of information is required by 37 CFR 1.16. 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 12 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.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Doc Code: DIST.E.FILE Document Description: Electronic Terminal Disclaimer - Filed	PTO/SB/25 PTO/SB/26 U.S. Patent and Trademark Office Department of Commerce

Electronic Petition Request	**TERMINAL DISCLAIMER TO OBVIATE A PROVISIONAL DOUBLE PATENTING REJECTION OVER A PENDING "REFERENCE" APPLICATION AND TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A "PRIOR" PATENT**
Application Number	15003327
Filing Date	21-Jan-2016
First Named Inventor	Fabio TRENTO
Attorney Docket Number	HHC002US6/CO001
Title of Invention	COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING

☒ 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
Helsinn Healthcare SA	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)

15003327 filed on 01/21/2016

15003327 filed on 01/21/2016

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) with 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)

9271975

9186357

8951969

8623826

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) is included with Electronic Terminal Disclaimer request.

○ I certify, in accordance with 37 CFR 1.4(d)(4), that the terminal disclaimer fee under 37 CFR 1.20(d) required for this terminal disclaimer has already been paid in the above-identified application.

Applicants claims the following fee status:

○ Small Entity

○ Micro Entity

◉ Regular Undiscounted

I hereby 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; 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.

THIS PORTION MUST BE COMPLETED BY THE SIGNATORY OR SIGNATORIES

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

  Registration Number 36942

- ( ) A sole inventor
- ( ) A joint inventor; I certify that I am authorized to sign this submission on behalf of all of the inventors as evidenced by the power of attorney in the application
- ( ) A joint inventor; all of whom are signing this request

Signature	/Clark G Sullivan/
Name	Clark Sullivan

*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.

Electronic Patent Application Fee Transmittal

Application Number:	15003327
Filing Date:	21-Jan-2016
Title of Invention:	COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING
First Named Inventor/Applicant Name:	Fabio TRENTO
Filer:	Clark G. Sullivan
Attorney Docket Number:	HHC002US6/CO001

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
STATUTORY OR TERMINAL DISCLAIMER	1814	1	160	160
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**160**

Doc Code: DISQ.E.FILE
Document Description: Electronic Terminal Disclaimer – Approved

Application No.: 15003327

Filing Date: 21-Jan-2016

Applicant/Patent under Reexamination: TRENTO

Electronic Terminal Disclaimer filed on December 1, 2016

☒ APPROVED

This patent is subject to a terminal disclaimer

☐ DISAPPROVED

Approved/Disapproved by: Electronic Terminal Disclaimer automatically approved by EFS-Web

U.S. Patent and Trademark Office

Electronic Acknowledgement Receipt

EFS ID:	27670307
Application Number:	15003327
International Application Number:	
Confirmation Number:	1097
Title of Invention:	COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING
First Named Inventor/Applicant Name:	Fabio TRENTO
Customer Number:	140619
Filer:	Clark G. Sullivan
Filer Authorized By:	
Attorney Docket Number:	HHC002US6/CO001
Receipt Date:	01-DEC-2016
Filing Date:	21-JAN-2016
Time Stamp:	17:43:41
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$160
RAM confirmation Number	120216INTEFSW17433900
Deposit Account	
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Electronic Terminal Disclaimer-Filed	eTerminal-Disclaimer.pdf	38058 fba2530297f9593add24e0e8396b0ec381957509	no	3
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30393 56369000e230e3893f80cc6e37ad87bbb30889da	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	68451		

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 a 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

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

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/003,327	01/21/2016	Fabio TRENTO	HHC002US6/CO001	1097

140619 7590 12/21/2016

Sullivan IP Solutions, LLC
PO Box 2252
New York, NY 10163

EXAMINER	
WEBB, WALTER E	

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
12/21/2016	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):

clark@sullivanipsolutions.com
docketing@sullivanipsolutions.com

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 15/003,327	**Applicant(s)** TRENTO ET AL.	
	Examiner WALTER WEBB	**Art Unit** 1612	**AIA (First Inventor to File) Status** No

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

THE REPLY FILED 29 November 2016 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

NO NOTICE OF APPEAL FILED

1. ☒ The reply was filed after a final rejection. No Notice of Appeal has been filed. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance;

(2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114 if this is a utility or plant application. Note that RCEs are not permitted in design applications. The reply must be filed within one of the following time periods:

a) ☒ The period for reply expires *3* months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action; or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

c) ☐ A prior Advisory Action was mailed more than 3 months after the mailing date of the final rejection in response to a first after-final reply filed within 2 months of the mailing date of the final rejection. The current period for reply expires months from the mailing date of *the prior Advisory Action* or SIX MONTHS from the mailing date of the final rejection, whichever is earlier.

Examiner Note: If box 1 is checked, check either box (a), (b) or (c). ONLY CHECK BOX (b) WHEN THIS ADVISORY ACTION IS THE FIRST RESPONSE TO APPLICANT'S FIRST AFTER-FINAL REPLY WHICH WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. ONLY CHECK BOX (c) IN THE LIMITED SITUATION SET FORTH UNDER BOX (c). See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) or (c) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendments filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);
   b) ☒ They raise the issue of new matter (see NOTE below);
   c) ☒ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: *See Continuation Sheet*. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).

5. ☐ Applicant's reply has overcome the following rejection(s): _____.

6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

7. ☒ For purposes of appeal, the proposed amendment(s): (a) ☒ will not be entered, or (b) ☐ will be entered, and an explanation of how the new or amended claims would be rejected is provided below or appended.

AFFIDAVIT OR OTHER EVIDENCE

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

9. ☐ The affidavit or other evidence filed after final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).

10. ☐ The affidavit or other evidence filed after the date of filing the Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing of good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).

11. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

12. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.

13. ☒ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). 11/29/16, 9/15/16

14. ☐ Other: _____.

STATUS OF CLAIMS

15. The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: .
Claim(s) objected to: .
Claim(s) rejected: 16-18,21,23-26 and 52-56.
Claim(s) withdrawn from consideration: .

/WALTER WEBB/
Primary Examiner, Art Unit 1612

Continuation of 3. NOTE: Applicant's proposed amendment "wherein said therapeutically efective dose consists of a singl dose of netupitant" constitutes new matter insofar as it is not supported by the disclosure. The examiner notes that the formulations of netupitant administered to patients includes other excipients. The amendment also raises other 112 issues such as written description, enablement, and indefiniteness.

Continuation of 12. does NOT place the application in condition for allowance because: Applicant's argument is not persuasive. Despite the teaching in Reddy to administer NK-1 antagonists for treating chemotherapy-induced nausea and vomiting, applicant argues, "Reddy does not mention that NK1 antagonists were developed primarily to treat emesis occuring during the delayed phase", or any dosing regimens for NKI antagonists. Applicant also argues that treatment during the acute phase is surprising and unexpected. The Examiner disagrees.

The prior art teaches treating 1-5 days after chemotherapy. Here the artisan has the option to administer the NK1 antagonist on day one as claimed. Note that the claimed method treats nausea and vomiting "for a period of five consecutive days" and states that this is "effective to treat nausea and vomiting during the acute and delayed phases of emesis". The treatment of acute and delayed phases appears to be a property of administering the NK1. The claims states that treatment is on day one but that does not necessarily exclude treatment on any other day of the five days. Again, because the prior art teaches treating 1-5 days, administration on day one would have been obvious.

In regard to dosing the point of administration is clear, treating nausea and vomiting. The atisan would have been expected to determine an effective amount. Established precedent holds, “[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results”. KSR Int’l Co. v. Teleflex Inc.,, 550 U.S. 398, 416 (2007). If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability.” Id. at 417. Moreover, the obviousness analysis is not limited to the explicit disclosures in prior art publications, but must also take account of what an ordinary artisan would reasonably infer from those disclosures.” Id. at 418.

Receipt date: 11/29/2016
Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
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.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	15003327
Filing Date	2016-01-21
First Named Inventor	TRENTO et al.
Art Unit	1612
Examiner Name	Walter E. Webb
Attorney Docket Number	HHC002

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Patent citation information please click the Add button. Add

U.S.PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Published Application citation information please click the Add button. Add

FOREIGN PATENT DOCUMENTS Remove

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1							

If you wish to add additional Foreign Patent Document citation information please click the Add button Add

NON-PATENT LITERATURE DOCUMENTS Remove

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, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /W.E.W/

Receipt date: 11/29/2016

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	15003327
Filing Date	2016-01-21
First Named Inventor	TRENTO et al.
Art Unit	1612
Examiner Name	Walter E. Webb
Attorney Docket Number	HHC002

	1	Emend Capsules and Emend for Oral Suspension: Prescribing information; 2003-2015 Merck Sharp & Dohme Corp. (Merck & Co., Inc.)
	2	Geling et al. Should 5-Hydroxytryptamine-3 Receptor Antagonists Be Administered Beyond 24 Hours After Chemotherapy to Prevent Delayed Emesis? Systematic Re-Evaluation of Clinical Evidence and Drug Cost Implications ; Journal of Clinical Oncology; Vol. 23(6) February 20, 2005; pp. 1289 - 1294.
	3	Hesketh et al. Differential involvement of neurotransmitters through the time course of cisplatin-induced emesis as revealed by therapy with specific receptor antagonists; European Journal of Cancer 39 (2003) 1074–1080.
	4	Prevention of chemotherapy- and radiotherapy-induced emesis: Results of the Perugia Consensus Conference; MASCC; Annals of Oncology 9: 811-819, 1998

If you wish to add additional non-patent literature document citation information please click the Add button [Add]

EXAMINER SIGNATURE

Examiner Signature	/WALTER E WEBB/	Date Considered	12/14/2016

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

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /W.E.W/

Receipt date: 09/15/2016
Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
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.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	15003327
Filing Date	2016-01-21
First Named Inventor	TRENTO et al.
Art Unit	1612
Examiner Name	Walter E. Webb
Attorney Docket Number	HHC002

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Patent citation information please click the Add button. Add

U.S.PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Published Application citation information please click the Add button. Add

FOREIGN PATENT DOCUMENTS Remove

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	2009-507933	JP		2009-02-26	Helsinn Healthcare SA	Corresponds to WO 2008049552 (previously cited)	X
	2	2007096763	WO		2007-08-30	PFIZER LIMITED	Corresponds to US 20090036459	☐
	3	2004045615	WO		2004-06-03	Helsinn Healthcare SA		☐

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /W.E.W/

Receipt date: 09/15/2016

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	15003327
Filing Date	2016-01-21
First Named Inventor	TRENTO et al.
Art Unit	1612
Examiner Name	Walter E. Webb
Attorney Docket Number	HHC002

	4	2011061622	WO	A1	2011-05-26	Helsinn Healthcare S.A.		☐

If you wish to add additional Foreign Patent Document citation information please click the Add button Add

NON-PATENT LITERATURE DOCUMENTS Remove

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, pages(s), volume-issue number(s), publisher, city and/or country where published.	T5
	1	Press Release, GSK provides update on regulatory filings for Zunrisa/Rezonic; Issued: Monday 28 September 2009, London UK.	
	2	WARR 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. (2005) J. Clin. Oncol. 23(12):2822-2830.	
	3	HERRINGTON et al., 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. (2008) Cancer 112(9):2080-2087.	
	4	YEO 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. (2009) Breast Cancer Res. Treat. 113:529-535.	
	5	LONGO et al., Palonosetron plus 3-day aprepitant and dexamethasone to prevent nausea and vomiting in patients receiving highly emetogenic chemotherapy. (2011) Support Care Cancer 19:1159-1164.	
	6	Press Release, NK1 receptor antagonist by Roche; Issued: Thursday, 23 February 2006, http://leaddiscovery.blogspot.com/2006/02/nk1-receptor-antagonist-by-roche.html (leaddiscovery.co.uk)	
	7	March 27, 2003, Approved FDA Prescribing Information for Emend	
	8	RUHLMANN, CHRISTINA et al., "Casopitant: a novel NK1-receptor antagonist in the prevention of chemotherapy-induced nausea and vomiting," Therapeutics and Clinical Risk Management, 2009:5 pp. 375-384	

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /W.E.W/

Receipt date: 09/15/2016

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	15003327
Filing Date	2016-01-21
First Named Inventor	TRENTO et al.
Art Unit	1612
Examiner Name	Walter E. Webb
Attorney Docket Number	HHC002

	9	PELLEGATII, MARIO et al., "Disposition and Metabolism of Radiolabeled Casopitant in Humans," Drug Metabolism 0 and Disposition, vol. 37, no. 8, 2009, pp.1635-1645
	10	HUANG, SHIH-CHUNG et al., "Neurokinin-1 receptor antagonists: a comprehensive patent survey," Expert Opin. Ther. 0 Patents (2010) 20(8), pp. 1019-1045
	11	REDDY, G. KESAVA et al., "Novel Neurokinin-1 Antagonists as Antiemetics for the Treatment of Chemotherapy-Induced Emesis," Supportive Cancer Therapy, April 1, 2006, LNKD-PUBMED: 18632487, vol. 3, no. 3, pp. 140-142, XP002626039, ISSN: 1543-2912
	12	DE WIT, R., "Current position of 5HT3 antagonists and the additional value of NK1 antagonists; a new class of antiemetics," British Journal of Cancer, June 16, 2003, LNKD-PUBMED: 12799621, vol. 88, no. 12, pp. 1823-1827, XP002626041, ISSN: 0007-0920
	13	DIEMUNSCH, P. et al., "Neurokinin-1 receptor antagonists in the prevention of postoperative nausea and vomiting," British Journal of Anaesthesia, July 2009, LNKD-PUBMED: 19454547, vol. 103, no. 1, pp. 7-13, XP002626040, ISSN: 1471-6771
	14	DIEMUNSCH, PIERRE et al., "Potential of Substance P Antagonists as Antiemetics," January 1,2003, Antiemetic Therapy, Basel [U.A.]: Karger, CH, pp. 78-97, XP008133831, ISBN: 978-3-8055-7547-8
	15	GRUNBERG, STEVEN M., 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: Official Journal of the Multinational Association of Supportive Care in Cancer, May 2009 LNKD-PUBMED: 19037667, vol. 17, no. 5, pp. 589-594, XP002626042, ISSN: 1433-7339
	16	STATHIS, MARIGO et al., "Inhibition of substance P-mediated responses in NG1 08- 15 celis by netupitant and palonosetron exhibit synergistic effects," European Journal of Pharmacology 689 (2012) pp. 25-30

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature	/WALTER E WEBB/	Date Considered	12/14/2016

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

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /W.E.W/

Docket No.: HHC002US6/CO001
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Trento et al.	)	Customer No.: 140619
Application No.: 15/003,327	)	Confirmation No.: 1097
Filing Date: 01-21-2016	)	Art Unit: 1612
For: COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING	)	Examiner: WEBB, WALTER E.

AMENDMENT AFTER FINAL

Commissioner for Patents
Alexandria, VA 22313-1450

DO NOT ENTER: /W.E.W/

Dear Sir:

In response to the Final Rejection notified in the above-referenced application on September 1, 2016, please enter the following amendments and consider the following remarks.

A REPLACEMENT CLAIM SET begins on page 2.

REMARKS begin on page 6.