PTO/SB/05 (08-08)
Approved for use through 06/30/2010. 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.	23278.20.US2
First Inventor	Fabio Trento
Title	Compositions and Methods For Treati
Express Mail Label No.	N/A - efiled on March 31, 2011

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

1. ☑ **Fee Transmittal Form** (e.g., PTO/SB/17)
2. ☑ **Applicant claims small entity status.** See 37 CFR 1.27.
3. ☑ **Specification** [*Total Pages* 35]
   Both the claims and abstract must start on a new page
   (For information on the preferred arrangement, see MPEP 608.01(a))
4. ☑ **Drawing(s)** (*35 U.S.C. 113*) [*Total Sheets* 5]
5. **Oath or Declaration** [*Total Sheets*]
   a. ☐ Newly executed (original or copy)
   b. ☐ A copy from a prior application (37 CFR 1.63(d))
   (for continuation/divisional with Box 18 completed)
   i. ☐ DELETION OF INVENTOR(S)
   Signed statement attached deleting inventor(s) name in the prior application, see 37 CFR 1.63(d)(2) and 1.33(b).
6. ☑ **Application Data Sheet.** See 37 CFR 1.76
7. ☐ **CD-ROM or CD-R** in duplicate, large table or Computer Program *(Appendix)*
   ☐ Landscape Table on CD
8. **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 PARTS

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

18. If a CONTINUING APPLICATION, *check appropriate box, and supply the requisite information below and in the first sentence of the specification following the title, or in an Application Data Sheet under 37 CFR 1.76:*

☑ Continuation ☐ Divisional ☐ Continuation-in-part (CIP) of prior application No.: PCT/US10/57192

Prior application information: *Examiner* NA *Art Unit:* NA

19. CORRESPONDENCE ADDRESS

☑ The address associated with Customer Number: 53449 ***OR*** ☐ Correspondence address below

Name					
Address					
City		State		Zip Code	
Country		Telephone		Email	

Signature	/Clark G. Sullivan/		Date	March 31, 2011	
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.

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:	Clark G. Sullivan/Pamela Mackey
Attorney Docket Number:	23278.20.US2

Filed as Small Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Utility filing Fee (Electronic filing)	4011	1	82	82
Utility Search Fee	2111	1	270	270
Utility Examination Fee	2311	1	110	110
Pages:				
Claims:				
Claims in excess of 20	2202	31	26	806
Independent claims in excess of 3	2201	3	110	330
Miscellaneous-Filing:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**1598**

Electronic Acknowledgement Receipt

EFS ID:	9785652
Application Number:	13077462
International Application Number:	
Confirmation Number:	5608
Title of Invention:	COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING
First Named Inventor/Applicant Name:	Fabio Trento
Customer Number:	53449
Filer:	Clark G. Sullivan/Pamela Mackey
Filer Authorized By:	Clark G. Sullivan
Attorney Docket Number:	23278.20.US2
Receipt Date:	31-MAR-2011
Filing Date:	
Time Stamp:	17:19:01
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$1598
RAM confirmation Number	4067
Deposit Account	
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

1	Fee Worksheet (PTO-875)	US2_2011_03_31_AMD_AFD_Fee_Transmittal.pdf	47500 6fb60d683d53b774b9df8d9890361398af0c7e05	no	2
Warnings:					
Information:					
2	Application Data Sheet	US2_2011_03_31_AMD_AFD_Application_Data_Sheet.pdf	1105243 3b6f3f0e35374b583b19fcfe73297edd7c31a352	no	6
Warnings:					
Information:					
3		US2_2011_03_31_AMD_AFD_Netupitant_emesis_nonprovisional_application.pdf	440788 c0f9ebfa351c56b8bfbed28fd97ea7ad22dacf30	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:					
4	Authorization for Extension of Time all replies	US2__2011_03_31_AMD_AFD_Authorization_to_Treat_Reply_Requiring_Extension_of_Time.pdf	3445 66e1b959f920c3abdacded9d797c3931f679d7e3	no	1
Warnings:					
Information:					
5	Transmittal of New Application	US2_2011_03_31_AMD_AFD_Utility_Application_Cover_Sheet.pdf	305328 a59885b44dcf38e5cabfb43eedef1d0875dcea05	no	2
Warnings:					
Information:					
6	Fee Worksheet (PTO-875)	fee-info.pdf	38162 c48334224fe87ad35b15520c56f5b4b318144ac1	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	1940466		

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/17 (10-08)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Effective on 12/08/2004.
Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).

FEE TRANSMITTAL
For FY 2009

☑ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 1598.00

Complete if Known	
Application Number	Not Yet Assigned
Filing Date	March 31, 2011
First Named Inventor	Fabio Trento
Examiner Name	Not Yet Assigned
Art Unit	Not Yet Assigned
Attorney Docket No.	23278.20.US2

METHOD OF PAYMENT (check all that apply)

☐ Check ☑ Credit Card ☐ Money Order ☐ None ☐ Other (please identify): _____

☐ Deposit Account Deposit Account Number: 504667 Deposit Account Name: Arnall Golden Gregory LLP

For the above-identified deposit account, the Director is hereby authorized to: (check all that apply)

☐ Charge fee(s) indicated below ☐ Charge fee(s) indicated below, except for the filing fee

☑ Charge any additional fee(s) or underpayments of fee(s) under 37 CFR 1.16 and 1.17 ☑ Credit any overpayments

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

FEE CALCULATION

1. BASIC FILING, SEARCH, AND EXAMINATION FEES

	FILING FEES		SEARCH FEES		EXAMINATION FEES		
		Small Entity		Small Entity		Small Entity	
Application Type	Fee ($)	Fee ($)	Fee ($)	Fee ($)	Fee ($)	Fee ($)	Fees Paid ($)
Utility	330	~~165~~ $82	540	270	220	110	$462.00
Design	220	110	100	50	140	70	
Plant	220	110	330	165	170	85	
Reissue	330	165	540	270	650	325	
Provisional	220	110	0	0	0	0	

2. EXCESS CLAIM FEES

Fee Description	Fee ($)	Small Entity Fee ($)
Each claim over 20 (including Reissues)	52	26
Each independent claim over 3 (including Reissues)	220	110
Multiple dependent claims	390	195

Total Claims	Extra Claims	Fee ($)	Fee Paid ($)
51 - 20 or HP =	31	x $26	= $806.00

HP = highest number of total claims paid for, if greater than 20.

Indep. Claims	Extra Claims	Fee ($)	Fee Paid ($)
6 - 3 or HP =	3	x $110	= $330.00

HP = highest number of independent claims paid for, if greater than 3.

Multiple Dependent Claims

Fee ($)	Fee Paid ($)

3. APPLICATION SIZE FEE

If the specification and drawings exceed 100 sheets of paper (excluding electronically filed sequence or computer listings under 37 CFR 1.52(e)), the application size fee due is $270 ($135 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).

Total Sheets	Extra Sheets	Number of each additional 50 or fraction thereof	Fee ($)	Fee Paid ($)
- 100 =	/ 50 =	(round up to a whole number)	x	=

4. OTHER FEE(S)

	Fees Paid ($)
Non-English Specification, $130 fee (no small entity discount)	
Other (e.g., late filing surcharge):	

SUBMITTED BY

Signature	/Clark G. Sullivan/	Registration No. (Attorney/Agent) 36,942	Telephone 404.873.8512
Name (Print/Type)	Clark G. Sullivan		Date March 31, 2011

This collection of information is required by 37 CFR 1.136. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, 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

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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/SB/14 (11-08)
Approved for use through 06/30/2010. 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	23278.20.US2
	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.)

Applicant Information:

Applicant 1 Remove

Applicant Authority ◉ Inventor ○ Legal Representative under 35 U.S.C. 117 ○ Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
	Fabio		Trento	

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

City	Parè (Como)	Country Of Residence[i]	IT
Citizenship under 37 CFR 1.41(b)[i]	IT		

Mailing Address of Applicant:

Address 1	Via Alla Valle 20B		
Address 2			
City	Parè (Como)	State/Province	
Postal Code	I-22020	Country[i]	IT

Applicant 2 Remove

Applicant Authority ◉ Inventor ○ Legal Representative under 35 U.S.C. 117 ○ Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
	Sergio		Cantoreggi	

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

City	Vezia	Country Of Residence[i]	CH
Citizenship under 37 CFR 1.41(b)[i]	CH		

Mailing Address of Applicant:

Address 1	Via ai Ronchi, 37		
Address 2			
City	Vezia	State/Province	
Postal Code	CH-6943	Country[i]	CH

Applicant 3 Remove

Applicant Authority ◉ Inventor ○ Legal Representative under 35 U.S.C. 117 ○ Party of Interest under 35 U.S.C. 118

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

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	23278.20.US2
	Application Number	
Title of Invention	Compositions and Methods for Treating Centrally Mediated Nausea and Vomiting	

Citizenship under 37 CFR 1.41(b) i	IT			
Mailing Address of Applicant:				
Address 1	Via della Libertà, 1A			
Address 2				
City	Cernobbio (Como)	**State/Province**		
Postal Code	I-22012	**Country**i	IT	

Applicant 4 Remove

Applicant Authority (•) Inventor ( ) Legal Representative under 35 U.S.C. 117 ( ) Party of Interest under 35 U.S.C. 118

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
Citizenship under 37 CFR 1.41(b) i	IT		
Mailing Address of Applicant:			
Address 1	Via Al Colle, 42		
Address 2			
City	I-21100	**State/Province**	
Postal Code	Varese	**Country**i	IT

Applicant 5 Remove

Applicant Authority (•) Inventor ( ) Legal Representative under 35 U.S.C. 117 ( ) Party of Interest under 35 U.S.C. 118

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
Citizenship under 37 CFR 1.41(b) i	IT		
Mailing Address of Applicant:			
Address 1	Via Ronco Capo Caccia, 32		
Address 2			
City	Casalzuigno (Varese)	**State/Province**	
Postal Code	I-21030	**Country**i	IT

Applicant 6 Remove

Applicant Authority (•) Inventor ( ) Legal Representative under 35 U.S.C. 117 ( ) Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
	Riccardo		Braglia	

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

City	Lugano-Pazzallo	**Country Of Residence**i	CH
Citizenship under 37 CFR 1.41(b) i	CH		

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	23278.20.US2
	Application Number	
Title of Invention	Compositions and Methods for Treating Centrally Mediated Nausea and Vomiting	

Mailing Address of Applicant:			
Address 1	Via Pian Scairolo 9		
Address 2			
City	Lugano-Pazzallo	**State/Province**	
Postal Code	CH-6912	**Country**[i]	CH

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	53449		
Email Address	agg.patent.docketing@agg.com	Add Email	Remove Email

Application Information:

Title of the Invention	Compositions and Methods for Treating Centrally Mediated Nausea and Vomiting		
Attorney Docket Number	23278.20.US2	**Small Entity Status Claimed**	☒
Application Type	Nonprovisional		
Subject Matter	Utility		
Suggested Class (if any)		**Sub Class (if any)**	
Suggested Technology Center (if any)			
Total Number of Drawing Sheets (if any)	5	**Suggested Figure for Publication (if any)**	

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).
Enter either Customer Number or complete the Representative Name section below. If both sections are completed the Customer Number will be used for the Representative Information during processing.

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

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	23278.20.US2
	Application Number	
Title of Invention	Compositions and Methods for Treating Centrally Mediated Nausea and Vomiting	

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, or 365(c) or indicate National Stage entry from a PCT application. Providing this 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(a)(2) or CFR 1.78(a)(4), and need not otherwise be made part of the specification.

Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	non provisional of	61262470	2009-11-18
Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	non provisional of	61382709	2010-09-14
Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	Continuation of	PCT/US10/57192	2010-11-19

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

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Remove

Application Number	Country [i]	Parent Filing Date (YYYY-MM-DD)	Priority Claimed
			◯ Yes ◯ No

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Assignee Information:

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Assignee 1 Remove

If the Assignee is an Organization check here. ☒			
Organization Name	Helsinn Healthcare SA		
Mailing Address Information:			
Address 1			
Address 2	P.O. Box 357		
City	Pambio-Noranco (Lugano)	**State/Province**	
Country [i] CH		Postal Code	CH-6915
Phone Number		Fax Number	
Email Address			

PTO/SB/14 (11-08)
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	23278.20.US2
	Application Number	
Title of Invention	Compositions and Methods for Treating Centrally Mediated Nausea and Vomiting	

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

Signature:

A signature of the applicant or representative is required in accordance with 37 CFR 1.33 and 10.18. Please see 37 CFR 1.4(d) for the form of the signature.

Signature	/Clark Sullivan/			Date (YYYY-MM-DD)	2011-03-31
First Name	Clark G.	Last Name	Sullivan	Registration Number	36942

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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; Riccardo Braglia, a citizen of Switzerland residing at Via Pian Scairolo 9 - CH-6912 Lugano-Pazzallo, Switzerland.

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

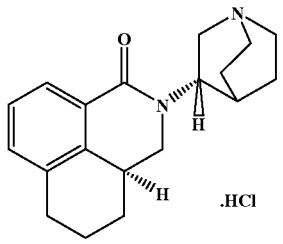
The present invention relates to the use of centrally acting NK_1 antagonists to treat nausea and vomiting, particular nausea and vomiting induced by highly emetogenic chemotherapy, and to the treatment of such nausea and vomiting over multiple consecutive days. The present invention also relates to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

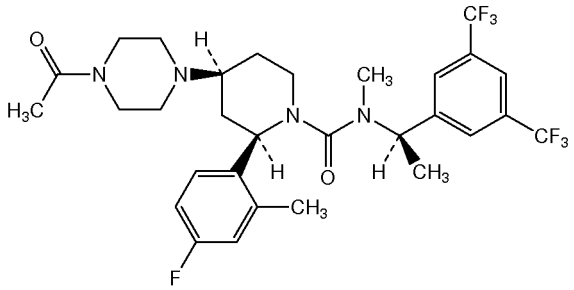


Methods of synthesizing palonosetron are described in U.S. Patent Nos. 5,202,333 and 5,510,486. Pharmaceutically acceptably dosage forms are described in PCT publications WO 2004/067005 and WO 2008/049552 from Helsinn Healthcare.

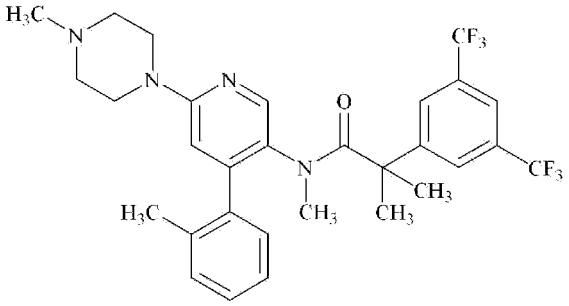
NK_1 antagonists have also recently emerged as a tool for combating nausea and vomiting from emetogenic medical procedures. Most recently, aprepitant was approved by the Food and Drug Administration ("FDA") for use in combination with other anti-emetic agents for the prevention of nausea and vomiting 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 $\geq$ 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	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.

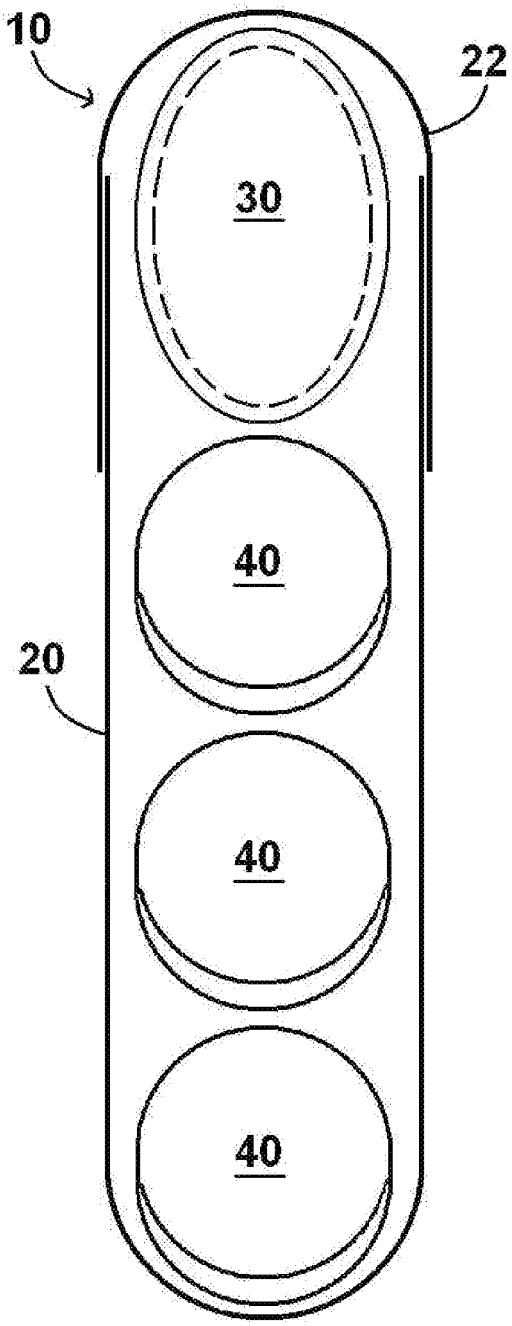


Figure 1

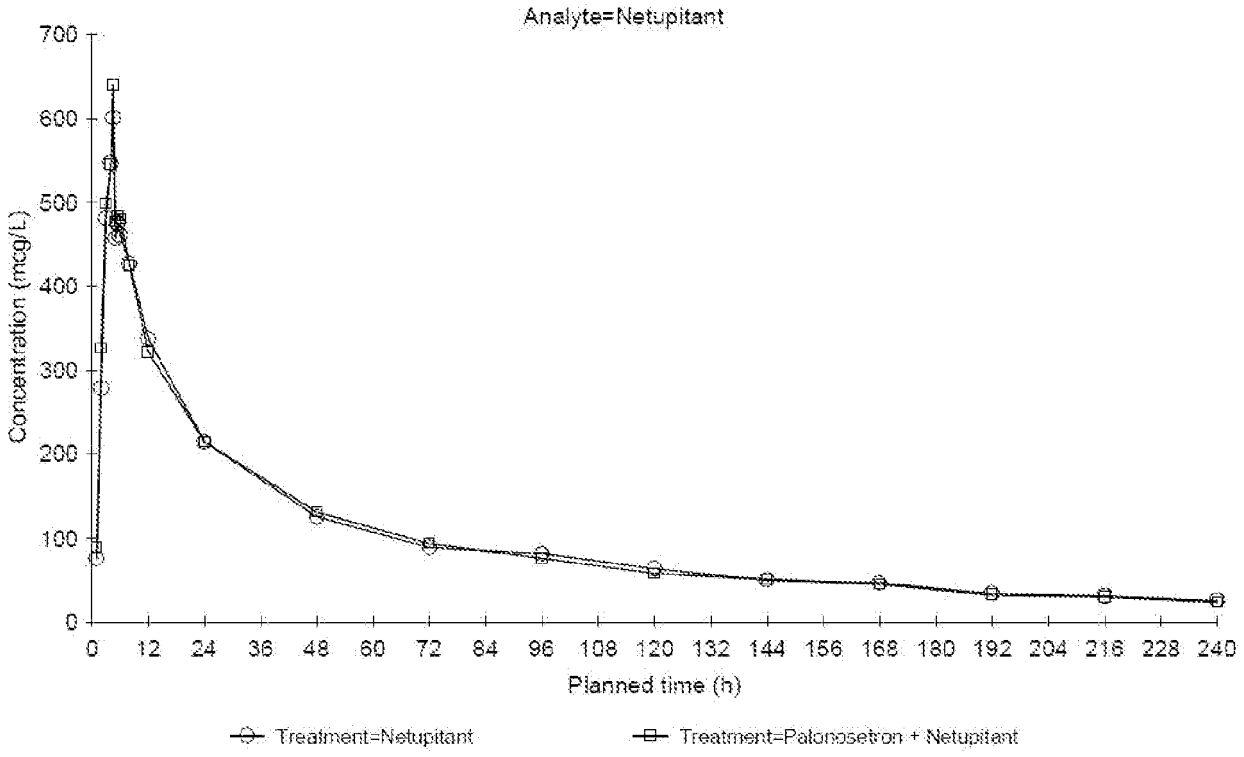

Analyte=Netupitant
Concentration (mcg/L)
700
600
500
400
300
200
100
0
0 12 24 36 48 60 72 84 96 108 120 132 144 156 168 180 192 204 216 228 240
Planned time (h)
Treatment=Netupitant
Treatment=Palonosetron + Netupitant

Figure 2

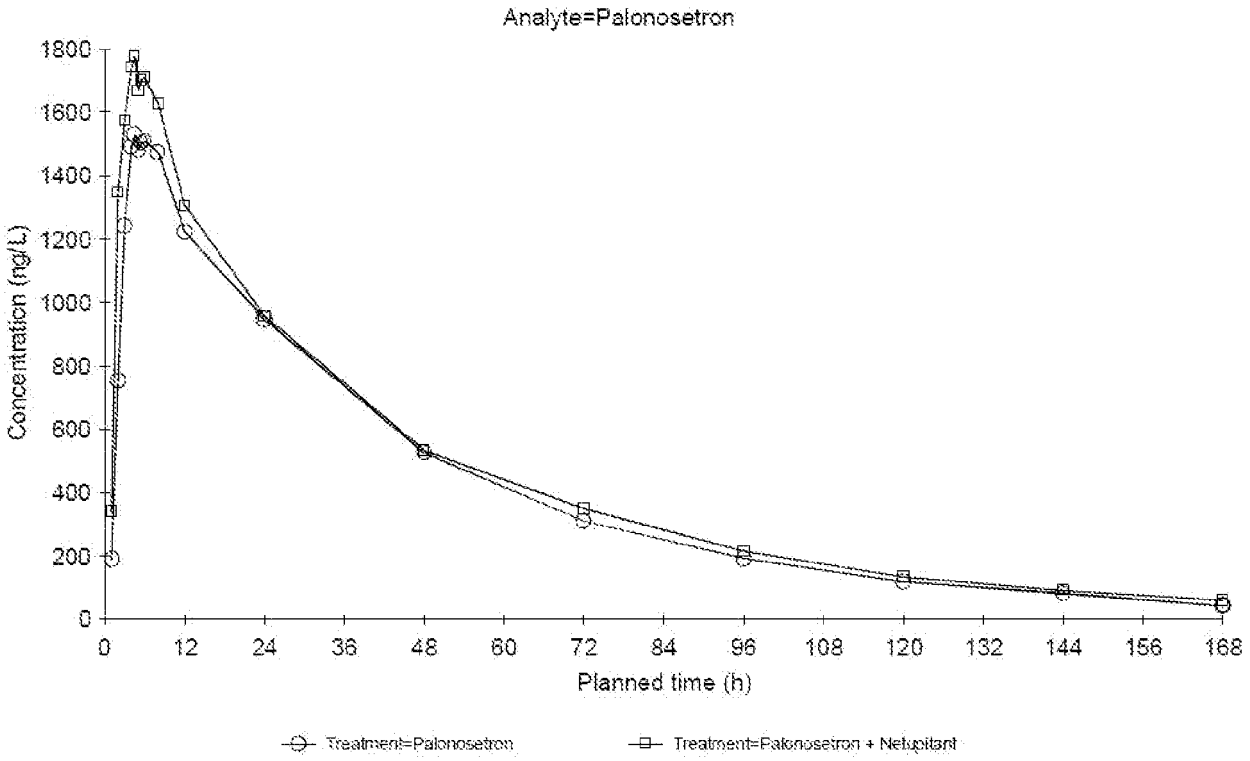

Analyte=Palonosetron
Concentration (ng/L)
1800
1600
1400
1200
1000
800
600
400
200
0
0
12
24
36
48
60
72
84
96
108
120
132
144
156
168
Planned time (h)
Treatment=Palonosetron
Treatment=Palonosetron + Netupitant

Figure 3

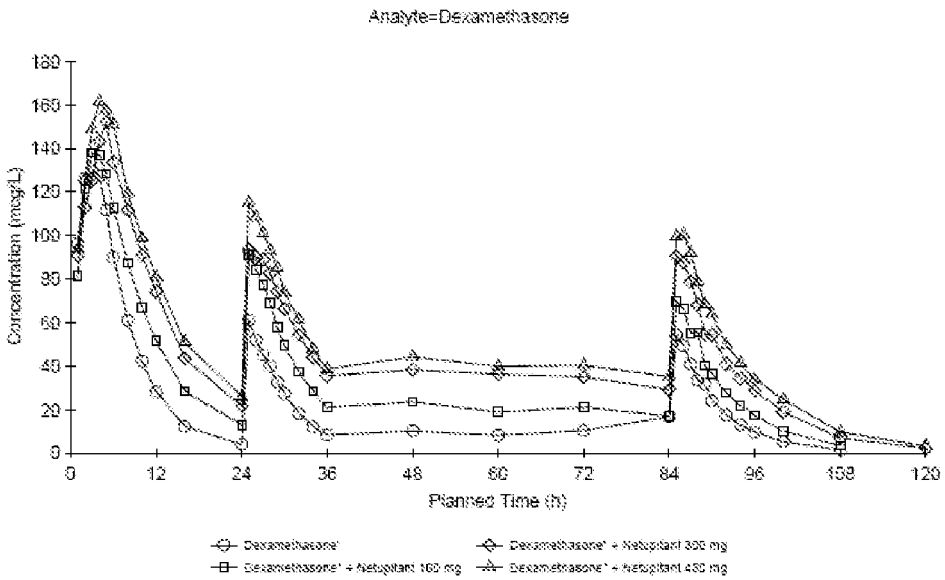


Figure 4: Dexamethasone Mean Plasma Concentrations Versus Time, With and Without Co-administration of Netupitant.

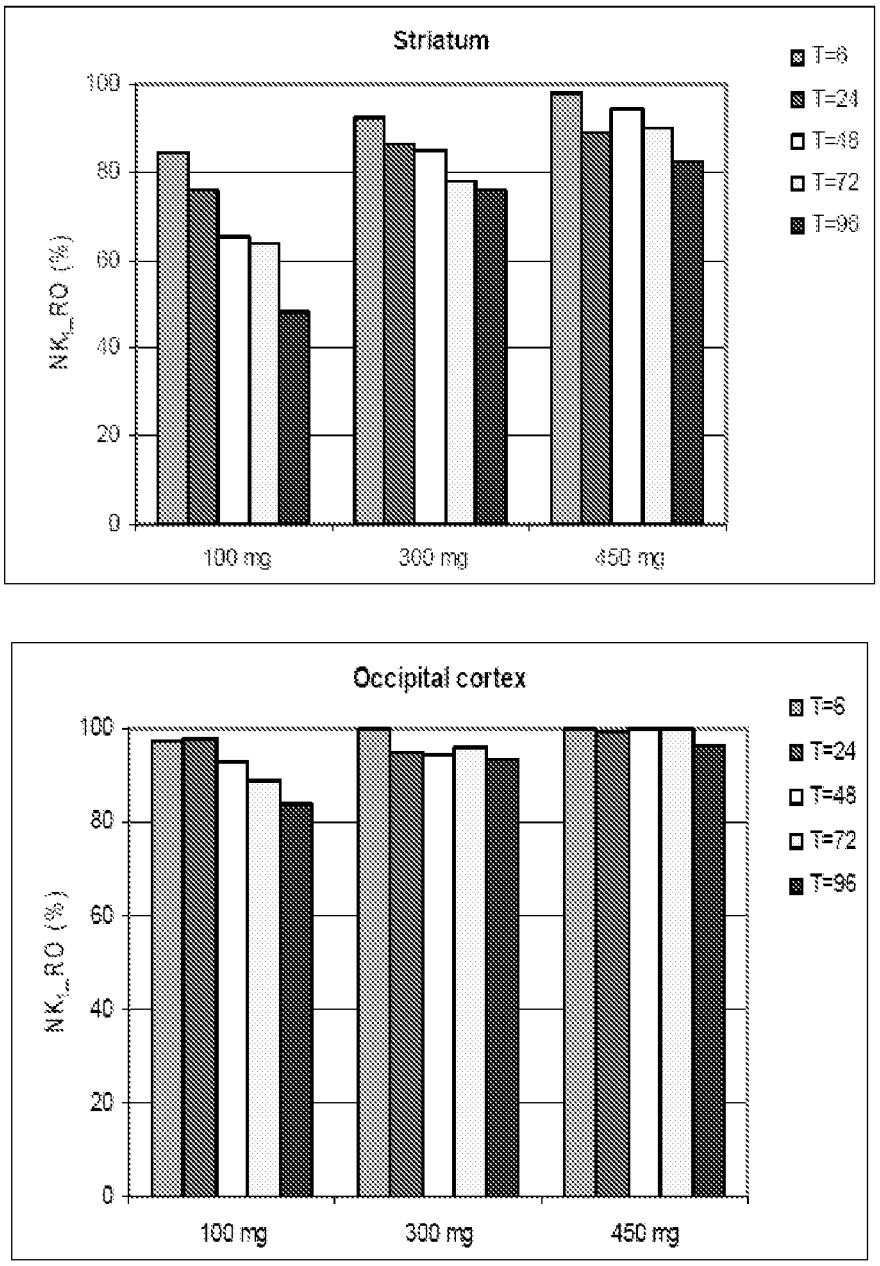


Figure 5: Average Neurokinin 1 Receptor Occupancy (NK_1-RO), Obtained at 6, 24, 48, 72 and 96 Hours after a Single Oral Dose of 100, 300 and 450 mg. netupitant (N=2 for each dose) in Striatum and Occipital Cortex, PET Study

CERTIFICATE OF ELECTRONIC TRANSMISSION UNDER 37 C.F.R. § 1.8

I hereby certify that this correspondence, including any items indicated as attached or included, is being transmitted to the United States Patent and Trademark Office via electronic transmission via EFS-Web on the date indicated below.

Date: March 31, 2011

/Pamela Mackey/
Pamela Mackey

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application: **Fabio Trento, et al.**	)	Art Unit: **Not Yet Assigned**
Application No. **Not Yet Assigned**	)	Examiner: **Not Yet Assigned**
Filed: **Filed Herewith**	)	Confirmation No.: **Not Yet Assigned**
For: **COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING**	)	

AUTHORIZATION TO TREAT REPLY REQUIRING EXTENSION OF TIME AS INCORPORATING PETITION FOR EXTENSION OF TIME

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

ARNALL GOLDEN GREGORY LLP
Customer Number 53449

Sir:

Pursuant to 37 C.F.R. §1.136(a)(3), the Commissioner is hereby requested and authorized to treat any concurrent or future reply in the above-identified application, requiring a petition for an extension of time for its timely submission, as incorporating a petition for extension of time for the appropriate length of time.

The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 50-4667.

Respectfully submitted,

/Clark G. Sullian/

Clark G. Sullivan
Registration No. 36,942

ARNALL GOLDEN GREGORY LLP
(404) 873-8500
(404) 873-8501 (fax)
Customer No.: 53449

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Application Number: 13077462 Document Date: 3/31/2011

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Electronic Acknowledgement Receipt

EFS ID:	9785652
Application Number:	13077462
International Application Number:	
Confirmation Number:	5608
Title of Invention:	COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING
First Named Inventor/Applicant Name:	Fabio Trento
Customer Number:	53449
Filer:	Clark G. Sullivan/Pamela Mackey
Filer Authorized By:	Clark G. Sullivan
Attorney Docket Number:	23278.20.US2
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Time Stamp:	17:19:01
Application Type:	Utility under 35 USC 111(a)

Adjustment date: 04/13/2011 CCETIN
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05 FC:2201 -330.00 OP

04/13/2011 CCETIN 00000022 504667 13077462

01 FC:2201 220.00 OP
02 FC:2202 20.00 DA 110.00 OP
03 FC:2203 195.00 DA

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
13/077,462	03/31/2011	1614	1813	23278.20.US2	51	5

CONFIRMATION NO. 5608

53449
PATENT CORRESPONDENCE
ARNALL GOLDEN GREGORY LLP
171 17TH STREET NW
SUITE 2100
ATLANTA, GA 30363

FILING RECEIPT

OC000000047141585

Date Mailed: 04/15/2011

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**

Applicant(s)

Fabio Trento, Pare (Como), ITALY;
Sergio Cantoreggi, Vezia, SWITZERLAND;
Giorgia Rossi, Cernobbio (Como), ITALY;
Roberta Cannella, Varese, ITALY;
Daniele Bonadeo, Casalzuigno (Varese), ITALY;
Riccardo Braglia, Lugano-Pazzallo, SWITZERLAND;

Assignment For Published Patent Application

HELSINN HEALTHCARE SA, Pambio-Noranco (Lugano), SWITZERLAND

Power of Attorney: None

Domestic Priority data as claimed by applicant

This appln claims benefit of 61/382,709 09/14/2010

Foreign Applications (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.)

If Required, Foreign Filing License Granted: 04/13/2011

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 13/077,462**

Projected Publication Date: To Be Determined - pending completion of Missing Parts

Non-Publication Request: No

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

Title

Compositions and Methods for Treating Centrally Mediated Nausea and Vomiting

Preliminary Class

514

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 (1-866-999-4158).

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).

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 13/077,462

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	82		N/A	
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	270		N/A	
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	110		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	56 minus 20 =	* 36	x 26 =	936	OR		
INDEPENDENT CLAIMS (37 CFR 1.16(h))	5 minus 3 =	* 2	x 110 =	220			
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $270 ($135 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))				195			
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	1813		TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

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
13/077,462	03/31/2011	Fabio Trento	23278.20.US2

CONFIRMATION NO. 5608

53449
PATENT CORRESPONDENCE
ARNALL GOLDEN GREGORY LLP
171 17TH STREET NW
SUITE 2100
ATLANTA, GA 30363

FORMALITIES LETTER

OC000000047141586

Date Mailed: 04/15/2011

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

Filing Date Granted

Items Required To Avoid Abandonment:

An application number and filing date have been accorded to this application. The item(s) indicated below, however, are missing. Applicant is given **TWO MONTHS** from the date of this Notice within which to file all required items below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- The oath or declaration is missing.
  A properly signed oath or declaration in compliance with 37 CFR 1.63, identifying the application by the above Application Number and Filing Date, is required.
  Note: If a petition under 37 CFR 1.47 is being filed, an oath or declaration in compliance with 37 CFR 1.63 signed by all available joint inventors, or if no inventor is available by a party with sufficient proprietary interest, is required.

The application is informal since it does not comply with the regulations for the reason(s) indicated below.

The required item(s) identified below must be timely submitted to avoid abandonment:

- Replacement drawings in compliance with 37 CFR 1.84 and 37 CFR 1.121(d) are required. The drawings submitted are not acceptable because:
  - The drawings contain excessive text. Suitable descriptive legends may be used, or may be required by the Examiner where necessary for understanding of the drawing but should contain as few words as possible (see 37 CFR 1.84(o)). See Figure(s) 5.
  - The drawings submitted to the Office are not electronically reproducible because portions of figures 2-4 are missing and/or blurry.

Applicant is cautioned that correction of the above items may cause the specification and drawings page count to exceed 100 pages. If the specification and drawings exceed 100 pages, applicant will need to submit the required application size fee.

The applicant needs to satisfy supplemental fees problems indicated below.

The required item(s) identified below must be timely submitted to avoid abandonment:

- A surcharge (for late submission of filing fee, search fee, examination fee or oath or declaration) as set forth in 37 CFR 1.16(f) of $**65** for a small entity in compliance with 37 CFR 1.27, must be submitted.

SUMMARY OF FEES DUE:

Total fee(s) required within **TWO MONTHS** from the date of this Notice is $**65** for a small entity
- $**65** Surcharge.

Replies should be mailed to:

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web.
https://sportal.uspto.gov/authenticate/AuthenticateUserLocalEPF.html

For more information about EFS-Web please call the USPTO Electronic Business Center at **1-866-217-9197** or visit our website at http://www.uspto.gov/ebc.

If you are not using EFS-Web to submit your reply, you must include a copy of this notice.

/tle/

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

MULTIPLE DEPENDENT CLAIM FEE CALCULATION SHEET

Substitute for Form PTO-1360
(For use with Form PTO/SB/06)

Application Number	Filing Date
13077462	

Applicant(s) Fabio Trento

* May be used for additional claims or amendments

CLAIMS	AS FILED		AFTER FIRST AMENDMENT		AFTER SECOND AMENDMENT	
	Indep	Depend	Indep	Depend	Indep	Depend
1	1					
2		1				
3		2				
4		(1)				
5		(1)				
6		(1)				
7		(1)				
8		(1)				
9		(1)				
10		(1)				
11		(1)				
12		(1)				
13		(1)				
14		(1)				
15		(1)				
16	1					
17		1				
18		2				
19		(1)				
20		(1)				
21		(1)				
22		(1)				
23		(1)				
24		(1)				
25		(1)				
26		(1)				
27	1					
28		1				
29		2				
30		(1)				
31		(1)				
32		(1)				
33		(1)				
34	1					
35		1				
36		2				
37		(1)				
38		(1)				
39		(1)				
40		(1)				
41		(1)				
42	1					
43		1				
44		2				
45		(1)				
46		(1)				
47		(1)				
48		(1)				
49		(1)				
50		(1)				
Total Indep	5		0		0	
Total Depend	51	↵	0	↵	0	↵
Total Claims	56		0		0	

CLAIMS	*		*		*	
	Indep	Depend	Indep	Depend	Indep	Depend
51		(1)				
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CERTIFICATE OF ELECTRONIC TRANSMISSION UNDER 37 C.F.R. § 1.8

I hereby certify that this correspondence, including any items indicated as attached or included, is being transmitted via electronic transmission via EFS-Web on the date indicated below.

Date: June 6, 2011

/Michelle D. Miller /

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application: **FABIO TRENTO et al.**	)	Art Unit: **1614**
Application No. **13/077462**	)	Examiner: **Not Yet Assigned**
Filed: **March 31, 2011**	)	Confirmation No.: **5608**
For: **COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING**	)	

RESPONSE TO THE NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION
(Filing Date Granted)

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

ARNALL GOLDEN GREGORY LLP
Customer Number 53449

Sir:

In response to the Notice to File Missing Parts of Nonprovisional Application mailed April 15, 2011 enclosed herewith for filing is:

1. Declaration signed by Fabio Trento, Sergio Cantoreggi, Giorgia Rossi, Roberta Cannella, Daniele Bonadeo, Riccardo Braglia; and
2. Replacement Drawings, Figures 2, 3, 4, and 5, in compliance with 37 CFR 1.84 and 37 CFR 1.121(d), correcting the deficiencies noted therein;

A deposit account charge is being electronically made in the amount of $65.00 concurrently and in connection with the filing of this response. This amount represents the surcharge for a small entity as set forth in 37 C.F.R. § 1.16(f) for late filing of the Declaration. Applicants believe that this amount is correct; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment, in connection with this response to Deposit Account No. 50-4667.

Respectfully submitted,

ARNALL GOLDEN GREGORY LLP

/Clark G. Sullivan/
Clark G. Sullivan.
Registration No. 36,942

ARNALL GOLDEN GREGORY LLP
(404) 873-8500
(404) 873-8501 (fax)
Customer No.: 53449

In re Application of: **Fabio TRENTO, Sergio CANTOREGGI, Giorgia ROSSI, Roberta CANNELLA, Daniele BONADEO and Riccardo BRAGLIA**

As a below named inventor, I hereby declare that my residence, post office address and citizenship are as stated below next to my name. I believe I am an original, first and joint inventor of the subject matter which is claimed and for which a patent is sought on the invention entitled **"COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING",** the specification of which was filed with the United States Patent and Trademark Office on **March 31, 2011**, as **U. S. Application No. 13/077,462.**

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above. I do not know and do not believe that the same was ever known or used by others in the United States of America before my or our invention thereof, or patented or described in any printed publication in any country before my or our invention thereof or more than one year prior to the date of this application. I further state that the invention was not in public use or on sale in the United States of America more than one year prior to the date of this application. *I understand that I have a duty of candor and good faith toward the Patent and Trademark Office,* and I acknowledge the duty to disclose information which is material to the patentability of this application in accordance with Title 37, Code of Federal Regulations, § 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, § 119 (a)-(d) of the foreign application(s) for patent or inventor's certificate listed below, and have also identified below any foreign application for patent or inventor's certificate disclosing subject matter in common with the above-identified specification and having a filing date before that of the application on which priority is claimed:

Application No.	Country	Filing Date	Priority Claimed Under 35 USC § 119 (a)-(d)
N/A			

I hereby claim the benefit under Title 35, United States Code, § 119(e) of any United States provisional application(s) listed below:

(Application No.)	(Filing Date)	(Application No.)	(Filing Date)
61/262,470	November 18, 2009	61/382,709	September 14, 2010

I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s) listed below and, insofar as the subject matter disclosed and claimed in the present application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code § 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, § 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application:

Application Serial No.	Filing Date	Status: patented, pending, abandoned
PCT/US10/57192	November 19, 2010	Pending

I further 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 statement 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 patents issuing thereon.

POWER OF ATTORNEY: I hereby appoint Clark G. Sullivan, Reg. No. 36,942, in addition to the practitioners associated with Customer Number **53449** to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith.

Send correspondence to: Clark G. Sullivan
Arnall Golden Gregory LLP
Customer No. 53449
171 17th Street, Suite 2100
Atlanta, Georgia 30363

Direct telephone calls to **(404) 873-8512**

Full name of first inventor: **Fabio TRENTO**	Citizenship: Italy
Inventor's signature Fabio Trento	Date: 9 May 2011
Residence and Post Office Address: **Via Alla Valle 20B I-22020 Parè (Como - Italy)**	

Full name of second inventor: **Sergio CANTOREGGI**	Citizenship: Switzerland
Inventor's signature S. Cantoreggi	Date: 10 May 2011
Residence and Post Office Address: ~~**Via Ai Ronchi, 37, Vezia, CH-6943, Switzerland**~~ **Via Sarone, 21 A, Cagiallo, CH 6955, Switzerland** SC, 10 May 2011	

Full name of second inventor: **Giorgia ROSSI**	Citizenship: Italy
Inventor's signature Giorgia Rossi	Date: 11-May-2011
Residence and Post Office Address: **Via della Libertà, 1A - I-22012 Cernobbio (Como - Italy)**	

Full name of second inventor: **Roberta CANNELLA**	Citizenship: Italy
Inventor's signature Roberta Cannella	Date: 12 - May - 2011
Residence and Post Office Address: **Via Al Colle, 42 - I-21100 Varese, Italy**	

Full name of second inventor: **Daniele BONADEO**	Citizenship: Italy
Inventor's signature Daniele Bonadeo	Date: 10/05/2011
Residence and Post Office Address: **Via Ronco Capo Caccia, 32 - I-21030 Casalzuigno, Varese, Italy**	

Full name of third inventor: **Riccardo BRAGLIA**	Citizenship: Switzerland
Inventor's signature	Date: 13 May 2011
Residence and Post Office Address: **Via Pian Scairolo 9, CH-6912 Lugano-Pazzallo, Switzerland**	

Electronic Patent Application Fee Transmittal

Application Number:	13077462
Filing Date:	31-Mar-2011
Title of Invention:	Compositions and Methods for Treating Centrally Mediated Nausea and Vomiting
First Named Inventor/Applicant Name:	Fabio Trento
Filer:	Clark G. Sullivan/Michelle Miller
Attorney Docket Number:	23278.20.US2

Filed as Small Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Late filing fee for oath or declaration	2051	1	65	65
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**65**

Electronic Acknowledgement Receipt

EFS ID:	10241445
Application Number:	13077462
International Application Number:	
Confirmation Number:	5608
Title of Invention:	Compositions and Methods for Treating Centrally Mediated Nausea and Vomiting
First Named Inventor/Applicant Name:	Fabio Trento
Customer Number:	53449
Filer:	Clark G. Sullivan/Michelle Miller
Filer Authorized By:	Clark G. Sullivan
Attorney Docket Number:	23278.20.US2
Receipt Date:	06-JUN-2011
Filing Date:	31-MAR-2011
Time Stamp:	16:21:27
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$65
RAM confirmation Number	3198
Deposit Account	504667
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

78

1	Drawings-only black and white line drawings	US__2011_06_06_OFA_AFD_Replacement_Drawings.pdf	234475 57a5592ea98ee4e14ae2d02c5579783701e75abf	no	4
Warnings:					
Information:					
2	Applicant Response to Pre-Exam Formalities Notice	US__2011_06_06_OFA_AFD_Missing_Parts_Transmittal_Letter.pdf	97684 e097b69f70e4955317ca51b6e10b94aff2b0be62	no	2
Warnings:					
Information:					
3	Oath or Declaration filed	US__2011_06_06_OFA_AFD_Executed_Declaration_.pdf	278295 f65f3dc13b022af4a6e1fa8f54dd05d47d3dac55	no	7
Warnings:					
Information:					
4	Fee Worksheet (SB06)	fee-info.pdf	29847 4f5faca0f3d0aabe311933897e8a0dd4bf6be78e	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	640301		

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.

<u>New Applications Under 35 U.S.C. 111</u>
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.

<u>National Stage of an International Application under 35 U.S.C. 371</u>
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.

<u>New International Application Filed with the USPTO as a Receiving Office</u>
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.

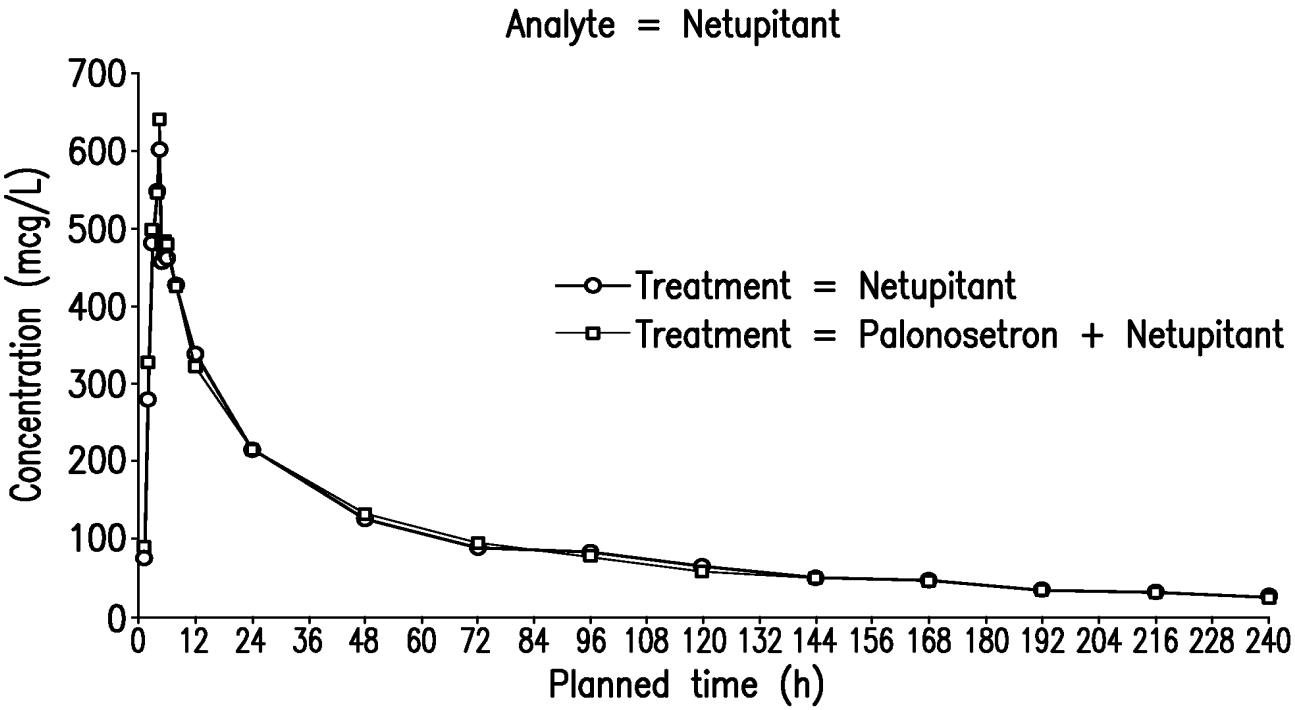

Analyte = Netupitant
Concentration (mcg/L)
700
600
500
400
300
200
100
0
0 12 24 36 48 60 72 84 96 108 120 132 144 156 168 180 192 204 216 228 240
Planned time (h)
Treatment = Netupitant
Treatment = Palonosetron + Netupitant

FIG.2

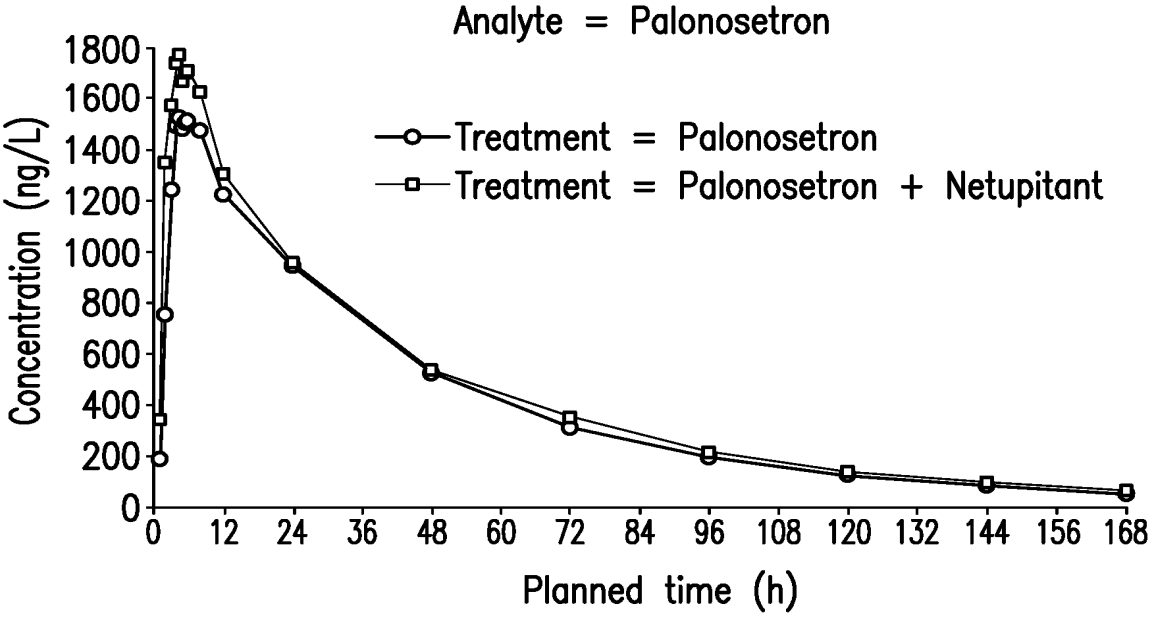

Analyte = Palonosetron
Treatment = Palonosetron
Treatment = Palonosetron + Netupitant
Concentration (ng/L)
1800
1600
1400
1200
1000
800
600
400
200
0
0
12
24
36
48
60
72
84
96
108
120
132
144
156
168
Planned time (h)

FIG.3

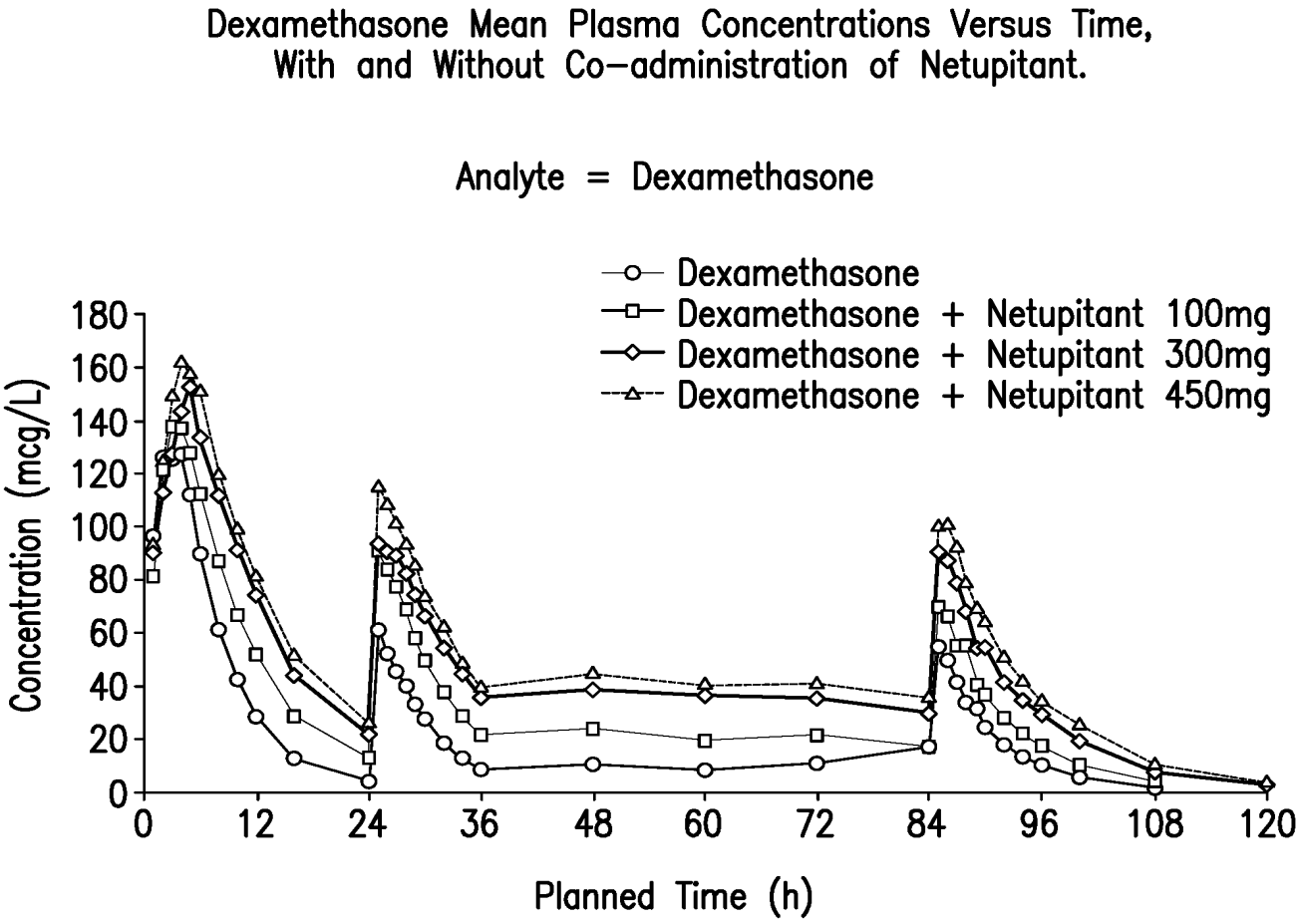

Dexamethasone Mean Plasma Concentrations Versus Time,
With and Without Co-administration of Netupitant.
Analyte = Dexamethasone
Dexamethasone
Dexamethasone + Netupitant 100mg
Dexamethasone + Netupitant 300mg
Dexamethasone + Netupitant 450mg
Concentration (mcg/L)
180
160
140
120
100
80
60
40
20
0
0
12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

FIG.4

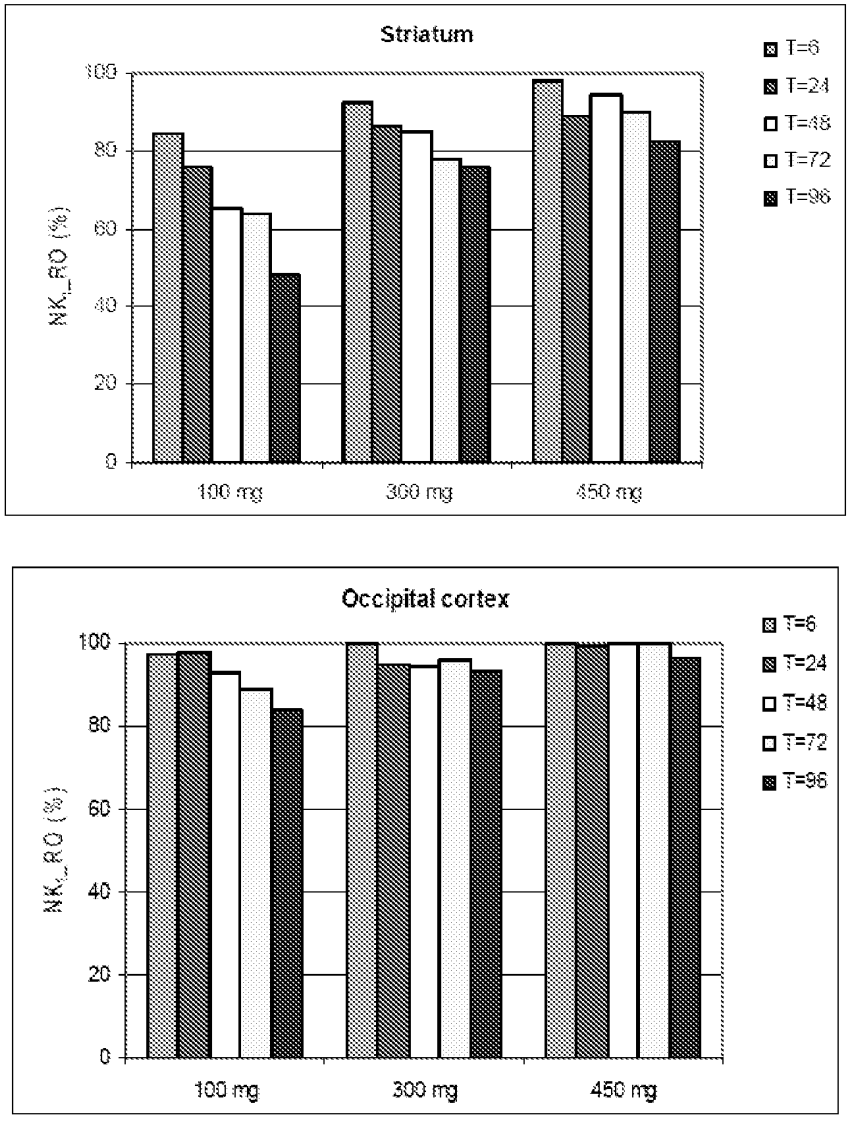

Striatum
NK_RO (%)
100
80
60
40
20
0
100 mg
300 mg
450 mg
T=6
T=24
T=48
T=72
T=96
Occipital cortex
NK_RO (%)
100
80
60
40
20
0
100 mg
300 mg
450 mg
T=6
T=24
T=48
T=72
T=96

FIG. 5

SCORE Placeholder Sheet for IFW Content

Application Number: 13077462 Document Date: 6/6/2011

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

- Drawings – Other than Black and White Line Drawings

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

To access the documents in the SCORE database, refer to instructions developed by SIRA.

At the time of document entry (noted above):

- Examiners may access SCORE content via the eDAN interface.
- Other USPTO employees can bookmark the current SCORE URL (http://es/ScoreAccessWeb/).
- External customers may access SCORE content via the Public and Private PAIR interfaces.

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 13/077,462

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	82		N/A	
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	270		N/A	
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	110		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	56 minus 20 =	* 36	x 26 =	936	OR		
INDEPENDENT CLAIMS (37 CFR 1.16(h))	5 minus 3 =	* 2	x 110 =	220			
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $270 ($135 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))				195			
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	1813		TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

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
13/077,462	03/31/2011	1614	1878	23278.20 (US2)	51	5

CONFIRMATION NO. 5608

UPDATED FILING RECEIPT

53449
PATENT CORRESPONDENCE
ARNALL GOLDEN GREGORY LLP
171 17TH STREET NW
SUITE 2100
ATLANTA, GA 30363



Date Mailed: 06/15/2011

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**

Applicant(s)

Fabio Trento, Pare (Como), ITALY;
Sergio Cantoreggi, Cagiallo, SWITZERLAND;
Giorgia Rossi, Cernobbio (Como), ITALY;
Roberta Cannella, Varese, ITALY;
Daniele Bonadeo, Casalzuigno, ITALY;
Riccardo Braglia, Lugano-Pazzallo, SWITZERLAND;

Assignment For Published Patent Application

HELSINN HEALTHCARE SA, Pambio-Noranco (Lugano), SWITZERLAND

Power of Attorney: The patent practitioners associated with Customer Number 53449

Domestic Priority data as claimed by applicant

This appln claims benefit of 61/382,709 09/14/2010

Foreign Applications (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.)

If Required, Foreign Filing License Granted: 04/13/2011

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 13/077,462**

Projected Publication Date: 03/15/2012

Non-Publication Request: No

Early Publication Request: No

** **SMALL ENTITY** **

Title

Compositions and Methods for Treating Centrally Mediated Nausea and Vomiting

Preliminary Class

514

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 (1-866-999-4158).

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

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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).

CERTIFICATE OF ELECTRONIC TRANSMISSION UNDER 37 C.F.R. § 1.8

I hereby certify that this correspondence, including any items indicated as attached or included, is being transmitted via electronic transmission via EFS-Web on the date indicated below.

Date: July 25, 2011

/Michelle D. Miller/
Michelle D. Miller

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application: **Fabio TRENTO et al.**	)	Art Unit: **Not Yet Assigned**
Application No. **13/077,462**	)	Examiner: **Not Yet Assigned**
Filed: **March 31, 2011**	)	Confirmation No.: **5608**
For: **COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING**	)	

REQUEST FOR CORRECTED FILING RECEIPT

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

ARNALL GOLDEN GREGORY LLP
Customer Number 53449

Sir:

In response to the Updated Filing Receipt mailed June 15, 2011, Applicants respectfully request that a corrected Filing Receipt be issued to reflect the correct priority data as filed in the Application Data Sheet and Declaration. Applicants would like to note that none of the inventors is a resident or national of the United States of America; therefore, upon receipt of International Application No. PCT/US10/57192 by the U. S. Receiving Office, the application was transferred to the International Bureau and re-assigned International Application No. PCT/IB2010/003106.

A copy of the Filing Receipt marked to show the corrections and the re-assigned international application number is attached.

It is believed that no additional fees are believed to be due; however, the Commissioner is hereby authorized to charge any deficiency or to credit any overpayment to Deposit Account No. 50-4667.

Respectfully submitted,

ARNALL GOLDEN GREGORY LLP

/Clark G. Sullivan/
Clark G. Sullivan
Reg. No.: 36,942

ARNALL GOLDEN GREGORY LLP
171 17th Street NW, Suite 2100
Atlanta, Georgia 30363
404-873-8512
404-873-8513
Customer No.: 53449

Filing Receipt - Marked to Show Corrections

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
13/077,462	03/31/2011	1614	1878	23278.20 (US2)	51	5

CONFIRMATION NO. 5608

UPDATED FILING RECEIPT



53449
PATENT CORRESPONDENCE
ARNALL GOLDEN GREGORY LLP
171 17TH STREET NW
SUITE 2100
ATLANTA, GA 30363

Date Mailed: 06/15/2011

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Applicant(s)

Fabio Trento, Pare (Como), ITALY;
Sergio Cantoreggi, Cagiallo, SWITZERLAND;
Giorgia Rossi, Cernobbio (Como), ITALY;
Roberta Cannella, Varese, ITALY;
Daniele Bonadeo, Casalzuigno, ITALY;
Riccardo Braglia, Lugano-Pazzallo, SWITZERLAND;

Assignment For Published Patent Application

HELSINN HEALTHCARE SA, Pambio-Noranco (Lugano), SWITZERLAND

Power of Attorney: The patent practitioners associated with Customer Number 53449

Domestic Priority data as claimed by applicant

This appln claims benefit of 61/382,709 09/14/2010 and claims benefit of 61/262,470 11/18/2009 and claims benefit of PCT/IB2010/003106 11/19/2010

Foreign Applications (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.)

If Required, Foreign Filing License Granted: 04/13/2011

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 13/077,462**

Projected Publication Date: 03/15/2012

Non-Publication Request: No

Early Publication Request: No

** **SMALL ENTITY** **

Title

Compositions and Methods for Treating Centrally Mediated Nausea and Vomiting

Preliminary Class

514

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

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LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

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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).

Electronic Acknowledgement Receipt

EFS ID:	10586755
Application Number:	13077462
International Application Number:	
Confirmation Number:	5608
Title of Invention:	Compositions and Methods for Treating Centrally Mediated Nausea and Vomiting
First Named Inventor/Applicant Name:	Fabio Trento
Customer Number:	53449
Filer:	Clark G. Sullivan/Michelle Miller
Filer Authorized By:	Clark G. Sullivan
Attorney Docket Number:	23278.20 (US2)
Receipt Date:	25-JUL-2011
Filing Date:	31-MAR-2011
Time Stamp:	13:16:34
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	Request for Corrected Filing Receipt	23278_20_US_2_Request_For_Corrected_Filing_Receipt.pdf	82619 fbf1c2db5de18877cd77c52787f7b9a34a825b66	no	2

Warnings:	
Information:	

2	Request for Corrected Filing Receipt	23278_20_US_2_Filing_Receipt_Marked_w_Changes.pdf	3489810 96afe429fdeb77393af4535105e30ab69a85b4a4	no	3

Warnings:	
Information:	
Total Files Size (in bytes):	3572429

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
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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/077,462	03/31/2011	Fabio Trento	23278.20 (US2)

CONFIRMATION NO. 5608

IMPROPER CFR REQUEST

53449
PATENT CORRESPONDENCE
ARNALL GOLDEN GREGORY LLP
171 17TH STREET NW
SUITE 2100
ATLANTA, GA 30363

OC000000048991154

Date Mailed: 07/29/2011

RESPONSE TO REQUEST FOR CORRECTED FILING RECEIPT

Continuity, Priority Claims, Petitions, and Non-Publication Requests

In response to your request for a corrected Filing Receipt, the Office is unable to comply with your request because:

- The application(s) to which priority is claimed were filed over a year prior to the filing date of this application. Therefore, the referenced application(s) cannot be claimed as domestic or foreign priority.

Prior-Filed Nonprovisional Application has been Improperly Indicated as a National Stage (35 U.S.C. 371) Application

Applicant submitted a benefit claim to a prior-filed nonprovisional application and improperly indicated that the prior-filed application is a national stage application under 35 U.S.C. 371. The Office's records show that the prior-filed application is an application filed under 35 U.S.C. 111(a). The Office has entered the benefit claim to the prior-filed application as a benefit claim to an application filed under 35 U.S.C. 111(a). Any request for a corrected filing receipt to include the indication that the prior-filed application is a national stage application will not be granted unless applicant supplies evidence that the prior application was in fact a national stage application. Accordingly, applicant should not submit such request without such evidence. Applicant should submit an amendment (or an application data sheet (ADS) if the benefit claim was submitted in an ADS) to delete the indication that the prior-filed application is a national stage application.

/hsarwari/

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

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COMMISSIONER FOR PATENTS
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PATENT CORRESPONDENCE
ARNALL GOLDEN GREGORY LLP
171 17TH STREET NW
SUITE 2100
ATLANTA, GA 30363

Courtesy Reminder for
Application Serial No: 13/077,462

Attorney Docket No: 23278.20 (US2)
Customer Number: 53449
Date of Electronic Notification: 07/29/2011

This is a courtesy reminder that new correspondence is available for this application. The official date of notification of the outgoing correspondence will be indicated on the form PTOL-90 accompanying the correspondence.

An email notification regarding the correspondence was sent to the following email address(es) associated with your customer number:
agg.patent.docketing@agg.com
Please verify that these email addresses are correct.

To view your correspondence online or update your email addresses, please visit us anytime at **https://sportal.uspto.gov/secure/myportal/privatepair.** If you have any questions, please email the Electronic Business Center (EBC) at EBC@uspto.gov or call 1-866-217-9197.

CERTIFICATE OF ELECTRONIC TRANSMISSION UNDER 37 C.F.R. § 1.8

I hereby certify that this correspondence, including any items indicated as attached or included, is being transmitted via electronic transmission via EFS-Web on the date indicated below.

Date: _August 18, 2011

/Michelle D. Miller/
Michelle D. Miller

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application: **Fabio TRENTO et al.**	)	Art Unit: **1615**
Application No. **13/077,462**	)	Examiner: **Not Yet Assigned**
Filed: **March 31, 2011**	)	Confirmation No.: **5608**
For: **COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING**	)	

PRELIMINARY AMENDMENT

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

Sir:

Prior to commencing examination of this application, please enter the amendments to the specification beginning on page 2.

AMENDMENTS TO THE SPECIFICATION

On page 1 please replace the paragraph after the title "CROSS-REFERENCE TO RELATED APPLICATIONS" with the following paragraph:

This application is a continuation of International Patent Application No. PCT/IB10/03106, 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~~ PCT/IB10/03106 are hereby incorporated herein by reference in their entirety.

CONCLUSION

To the extent any additional fee is owed for this submission, the Commissioner is authorized to charge Deposit Account Number 504667.

Respectfully submitted,

/Clark G. Sullivan/
Clark G. Sullivan
Reg. No. 36,942

Arnall Golden Gregory LLP
171 17th Street NW
Suite 2100
Atlanta, Georgia 30363
404.873.8186

AGG Docket: 23278.20.US2

COPY FOR RO/US PCT PCT/US2010/057192 07.01.2011 IAMS

IAP11Rec'd PCT 07 JAN 2011

PATENT COOPERATION TREATY

From the: RECEIVING OFFICE

To:

SULLIVAN, Clark, G.
Arnall Golden Gregory Llp
171 17th Street, Nw, Suite 2100
Altanta, GA 30363-1031
ETATS-UNIS D'AMERIQUE
Facsimile No.: 404-873-8513

PCT

COMMUNICATION IN CASES FOR WHICH NO OTHER FORM IS APPLICABLE

Date of mailing *(day/month/year)* 06 December 2010 (06.12.2010)	
REPLY DUE See paragraph 1 below	Applicant's or agent's file reference 23278.20
International application No. PCT/IB2010/003106	International filing date *(day/month/year)* 18 November 2010 (18.11.2010)
Applicant HELSINN HEALTHCARE S.A.	

1. ☐ REPLY DUE within from the above date of mailing
   ☐ NO REPLY DUE, however, see below
   ☒ IMPORTANT COMMUNICATION
   ☐ INFORMATION ONLY

2. COMMUNICATION:

A. NOTIFICATION OF RECEIPT OF PURPORTED INTERNATIONAL APPLICATION BY INTERNATIONAL BUREAU ACTING AS RECEIVING OFFICE (PCT Rule 19.4(a)(i))

The applicant is hereby notified that the International Bureau of WIPO has received on 26 November 2010 (26.11.2010) the above-mentioned purported international application (reference PCT/US2010/057192) from the United States Patent and Trademark Office (USPTO) which is not competent under PCT Rule 19.1 or 19.2 (having regard to the applicant's nationality or residence) to receive that international application.

According to PCT Rule 19.4(b), this international application is considered to have been received by the International Bureau **as receiving Office (RO/IB) under PCT Rule 19.1(a)(iii) on the date of receipt of the international application by the USPTO (18 November 2010 (18.11.2010)).**

Any future correspondence in connection with this international application must indicate the international application number assigned by RO/IB (PCT/IB2010/003106).

Note that any communication (i) intended for the receiving Office must now be sent direct to the International Bureau of WIPO at the address indicated below, (ii) relating to international preliminary examination under Chapter II, including the demand, must be submitted direct to the International Preliminary Examining Authority concerned.

A copy of this notification is being sent to the USPTO.

/...

Name and mailing address of the receiving Office: The International Bureau of WIPO PCT Receiving Office Section 34, chemin des Colombettes, 1211 Geneva 20, Switzerland Facsimile No. +41 22 910 06 10 (RPT)	Authorized officer No. Vivet Jean-Marc E-mail ro.ib@wipo.int Telephone No. +4122 338 9895

ANNEX TO FORM PCT/RO/132

International application No.
PCT/IB2010/003106

B. MATTERS CONCERNING THE RIGHT TO REPRESENT THE APPLICANT(S)

In addition, it seems that the person indicated in Box IV of the request form does not have the right to practice before the national Office of the Contracting State of which the applicant is a resident or national, and thus does not have the right to practice before the International Bureau as receiving Office (RO/IB) in respect of the above-mentioned international application (PCT Rule 83.1bis(a)).

The indication given in Box IV of the request form will therefore be treated as a special address to which correspondence will be sent.

Any further communication from the applicant to the receiving Office and other International Authorities (except payment of fees) **will have to be signed by the applicant himself or by a duly appointed agent who has the right to practice before RO/IB, in respect of the above-mentioned international application,** (that is, a person who has the right to practice before either the Swiss Federal Institute of Intellectual Property, the European Patent Office (EPO) or the Italian Patent and Trademark Office (see PCT Rules 90.3(a) and 92.1).

C. MATTERS CONCERNING THE CHOICE OF INTERNATIONAL SEARCHING AUTHORITY

The applicant is hereby informed that, where an international application is filed with the International Bureau as receiving Office, the competent International Searching Authority(ies) is (are) that (those) which would have been competent if said international application had been filed with a competent national (or regional) Office as receiving Office (see PCT Rule 35).

As a result, the only competent International Searching Authority, in the present case, is the European Patent Office (ISA/ EP).

PATENT COOPERATION TREATY

From the RECEIVING OFFICE

To:

CLARK G. SULLIVAN
ARNALL GOLDEN GREGORY LLP
171 17TH STREET, NW, SUITE 2100
ALTANTA, GEORGIA 30363-1031

Confirmation No: 5395

PCT

NOTIFICATION OF TRANSMITTAL OF PURPORTED INTERNATIONAL APPLICATION TO THE INTERNATIONAL BUREAU AS RECEIVING OFFICE AND INVITATION TO PAY FEE

(PCT Rule 19.4(a)(i) and (ii) and Administrative Instructions, Section 333)

	Date of mailing *(day/month/year)*: 24 Nov 2010
Applicant's or agent's file reference: 23278.20	**REPLY DUE**: 15 days from the above date of mailing (only if item 3 applies)
Receiving Office reference/International application No.: PCT/US2010/057192	Date of receipt of the purported international application *(day/month/year)*: 18 Nov 2010
Applicant: HELSINN HEALTHCARE S.A.	

1. The applicant is hereby **notified** that:
   - ☒ this receiving Office is not competent, on account of the **nationality and residence** of the applicant, to receive the international application (Rule 19.1 or 19.2).
   - ☐ the international application is not in a **language** accepted by this receiving Office under Rule 12.1(a) but is in a language accepted by the International Bureau as receiving Office.
2. Consequently, the international application **is considered to have been received by this receiving Office on behalf of the International Bureau as receiving Office** on the date of receipt indicated above, and is or will be promptly transmitted to it.
3. ☒ The transmittal to the International Bureau as receiving Office is subject to the payment of a fee in the amount of:

   $240.00

   - ☒ The fee will be deducted from any fee already paid to this receiving Office.
   - ☐ The applicant is hereby **invited to pay** that fee within the time limit indicated above.

   Failure to pay that fee may result in the international application not being transmitted to the International Bureau as receiving Office.
4. Any fees paid by the applicant will be refunded in due course, except, where applicable, the above-mentioned fee payable to this Office under Rule 19.4(b) (see item 3).
5. The transmittal fee, the international filing fee and the search fee are payable to the International Bureau as receiving Office, in a currency prescribed by it within a time limit of one month from the actual date of receipt of the international application by the International Bureau as receiving Office (rather than one month from the date of receipt of the international application indicated above).
6. **ATTENTION:** If the applicant has requested this receiving Office to prepare and transmit to the International Bureau a certified copy of any earlier application the priority of which is claimed by marking the check-box provided for in Box No. VI of the request (see Rule 17.1(b)), it remains the applicant's responsibility to submit such certified copy to the International Bureau, or to the International Bureau as receiving Office, within the time limit under Rule 17.1(a).
7. A copy of this notification is being sent to the International Bureau as receiving Office together with the above-mentioned international application.

Name and mailing address of the receiving Office	Authorized officer
Mail Stop PCT, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450	Catherine Williams
Facsimile No. 571-273-3201	Telephone No. 571-272-0436

Form PCT/RO/151 (January 2004)

Electronic Acknowledgement Receipt

EFS ID:	10763915
Application Number:	13077462
International Application Number:	
Confirmation Number:	5608
Title of Invention:	Compositions and Methods for Treating Centrally Mediated Nausea and Vomiting
First Named Inventor/Applicant Name:	Fabio Trento
Customer Number:	53449
Filer:	Clark G. Sullivan/Michelle Miller
Filer Authorized By:	Clark G. Sullivan
Attorney Docket Number:	23278.20 (US2)
Receipt Date:	18-AUG-2011
Filing Date:	31-MAR-2011
Time Stamp:	12:42:44
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	Request for Corrected Filing Receipt	23278_20_US_2_Request_For_Corrected_Filing_Receipt.pdf	83207 bc2b17a1e52acd4ef6c5f7dd6b1a36494cc50f1c	no	2

Warnings:	
Information:	

2	Application Data Sheet	23278_20_US_2_Supplemental_Application_Data_Sheet.pdf	1180383 f569d04b706f07bdc16e3bb378faea5ee548c6a7	no	6
Warnings:					
Information:					
This is not an USPTO supplied ADS fillable form					
3	Preliminary Amendment	23278_20_US_2_Preliminary_Amendment.pdf	103229 d17719bd18523e59a99a3fd25584ccd83791275a	no	3
Warnings:					
Information:					
4	Miscellaneous Incoming Letter	23278_20_US_2_Documents_Submitted_with_Request_For_Corrected_Filing_Receipt.pdf	2337567 038db6e1a42c2b30bfd1c18a8c00f70b6148fb77	no	3
Warnings:					
Information:					
		Total Files Size (in bytes):	3704386		

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.

<u>New Applications Under 35 U.S.C. 111</u>
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.

<u>National Stage of an International Application under 35 U.S.C. 371</u>
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.

<u>New International Application Filed with the USPTO as a Receiving Office</u>
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.

CERTIFICATE OF ELECTRONIC TRANSMISSION UNDER 37 C.F.R. § 1.8

I hereby certify that this correspondence, including any items indicated as attached or included, is being transmitted via electronic transmission via EFS-Web on the date indicated below.

Date: August 18, 2011

/Michelle D. Miller/
Michelle D. Miller

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application: **Fabio TRENTO et al.**	)	Art Unit: **1615**
Application No. **13/077,462**	)	Examiner: **Not Yet Assigned**
Filed: **March 31, 2011**	)	Confirmation No.: **5608**
For: **COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING**	)	

REQUEST FOR CORRECTED FILING RECEIPT

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

ARNALL GOLDEN GREGORY LLP
Customer Number 53449

Sir:

Applicants respectfully request that a corrected Filing Receipt be issued to reflect the correct priority data as noted in the Supplemental Application Data Sheet and Preliminary Amendment filed concurrently herewith.

Applicant respectfully notes that U.S. Application No. 13/077,462 is a 35 U.S.C. §120 continuation of International Application No. PCT/US10/57192 filed November 18, 2010. Upon receipt of International Application No. PCT/US10/57192 by the U. S. Receiving Office, the receiving

office informed the Applicant that it was not competent to receive the international application on account of the nationality and residence of the applicant; consequently, the U. S. Receiving Office transferred the application to the International Bureau and the application was re-assigned International Application No. PCT/IB10/03106 and accorded an international filing date of November 18, 2010. A copy of Form PCT/RO/151 "Notification of Transmittal of Purported International Application to the International Bureau as Receiving Office and Invitation to Pay Fee" is attached.

The re-assigned International Application No. PCT/IB10/03106 and the International Filing Date of November 18, 2010 are correctly noted on the Supplemental Application Data Sheet and Preliminary Amendment.

It is believed that no additional fees are believed to be due; however, the Commissioner is hereby authorized to charge any deficiency or to credit any overpayment to Deposit Account No. 50-4667.

Respectfully submitted,
ARNALL GOLDEN GREGORY LLP

/Clark G. Sullivan/
Clark G. Sullivan
Reg. No.: 36,942

ARNALL GOLDEN GREGORY LLP
171 17th Street NW, Suite 2100
Atlanta, Georgia 30363
404-873-8512
404-873-8513
Customer No.: 53449

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	23278.20.US2
	Application Number	13/077,462
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.)

Applicant Information:

Applicant 1 Remove

Applicant Authority ◉ Inventor ○ Legal Representative under 35 U.S.C. 117 ○ Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
	Fabio		Trento	

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

City	Parè (Como)	Country Of Residence[i]	IT

Citizenship under 37 CFR 1.41(b)[i] IT

Mailing Address of Applicant:

Address 1	Via Alla Valle 20B		
Address 2			
City	Parè (Como)	State/Province	
Postal Code	I-22020	Country[i]	IT

Applicant 2 Remove

Applicant Authority ◉ Inventor ○ Legal Representative under 35 U.S.C. 117 ○ Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
	Sergio		Cantoreggi	

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

City	Vezia	Country Of Residence[i]	CH

Citizenship under 37 CFR 1.41(b)[i] CH

Mailing Address of Applicant:

Address 1	Via ai Ronchi, 37		
Address 2			
City	Vezia	State/Province	
Postal Code	CH-6943	Country[i]	CH

Applicant 3 Remove

Applicant Authority ◉ Inventor ○ Legal Representative under 35 U.S.C. 117 ○ Party of Interest under 35 U.S.C. 118

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

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	23278.20.US2
	Application Number	13/077,462
Title of Invention	Compositions and Methods for Treating Centrally Mediated Nausea and Vomiting	

Citizenship under 37 CFR 1.41(b) i	IT		
Mailing Address of Applicant:			
Address 1	Via della Libertà, 1A		
Address 2			
City	Cernobbio (Como)	**State/Province**	
Postal Code	I-22012	**Country**i	IT

Applicant 4 Remove

Applicant Authority ◉ Inventor	○ Legal Representative under 35 U.S.C. 117	○ Party of Interest under 35 U.S.C. 118	
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
Citizenship under 37 CFR 1.41(b) i	IT		
Mailing Address of Applicant:			
Address 1	Via Al Colle, 42		
Address 2			
City	I-21100	**State/Province**	
Postal Code	Varese	**Country**i	IT

Applicant 5 Remove

Applicant Authority ◉ Inventor	○ Legal Representative under 35 U.S.C. 117	○ Party of Interest under 35 U.S.C. 118	
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
Citizenship under 37 CFR 1.41(b) i	IT		
Mailing Address of Applicant:			
Address 1	Via Ronco Capo Caccia, 32		
Address 2			
City	Casalzuigno (Varese)	**State/Province**	
Postal Code	I-21030	**Country**i	IT

Applicant 6 Remove

Applicant Authority ◉ Inventor	○ Legal Representative under 35 U.S.C. 117	○ Party of Interest under 35 U.S.C. 118	
Prefix	**Given Name**	**Middle Name**	**Family Name** / **Suffix**
	Riccardo		Braglia

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

City	Lugano-Pazzallo	**Country Of Residence**i	CH
Citizenship under 37 CFR 1.41(b) i	CH		

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	23278.20.US2
	Application Number	13/077,462
Title of Invention	Compositions and Methods for Treating Centrally Mediated Nausea and Vomiting	

Mailing Address of Applicant:			
Address 1	Via Pian Scairolo 9		
Address 2			
City	Lugano-Pazzallo	State/Province	
Postal Code	CH-6912	Country[i]	CH

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	53449		
Email Address	agg.patent.docketing@agg.com	Add Email	Remove Email

Application Information:

Title of the Invention	Compositions and Methods for Treating Centrally Mediated Nausea and Vomiting		
Attorney Docket Number	23278.20.US2	Small Entity Status Claimed	☒
Application Type	Nonprovisional		
Subject Matter	Utility		
Suggested Class (if any)		Sub Class (if any)	
Suggested Technology Center (if any)			
Total Number of Drawing Sheets (if any)	5	Suggested Figure for Publication (if any)	

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).
Enter either Customer Number or complete the Representative Name section below. If both sections are completed the Customer Number will be used for the Representative Information during processing.

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

Supplemental Application Data Sheet

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	23278.20.US2
	Application Number	13/077,462
Title of Invention	Compositions and Methods for Treating Centrally Mediated Nausea and Vomiting	

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, or 365(c) or indicate National Stage entry from a PCT application. Providing this 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(a)(2) or CFR 1.78(a)(4), and need not otherwise be made part of the specification.

Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	non provisional of	61262470	2009-11-18
Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	non provisional of	61382709	2010-09-14
Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	Continuation of	~~PCT/US10/57102~~PCT/IB10/03106	~~2010-11-19~~ 2010-11-18

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

Foreign Priority Information:

This section allows for the applicant to claim benefit of foreign priority and to identify any prior foreign application for which priority is not claimed. 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(a).

Remove

Application Number	Country [i]	Parent Filing Date (YYYY-MM-DD)	Priority Claimed
			◯ Yes ◯ No

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

Assignee Information:

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

Assignee 1 Remove

If the Assignee is an Organization check here.	☒		
Organization Name	Helsinn Healthcare SA		
Mailing Address Information:			
Address 1			
Address 2	P.O. Box 357		
City	Pambio-Noranco (Lugano)	**State/Province**	
Country [i] CH		Postal Code	CH-6915
Phone Number		Fax Number	
Email Address			

PTO/SB/14 (11-08)
Approved for use through 08/30/2010. 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	23278.20.US2
	Application Number	13/077,462
Title of Invention	Compositions and Methods for Treating Centrally Mediated Nausea and Vomiting	

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

Signature:

A signature of the applicant or representative is required in accordance with 37 CFR 1.33 and 10.18. Please see 37 CFR 1.4(d) for the form of the signature.

Signature	/Clark Sullivan/			Date (YYYY-MM-DD)	2011-03-31
First Name	Clark G.	Last Name	Sullivan	Registration Number	36942

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 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.

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
13/077,462	03/31/2011	

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	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			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 $250 ($125 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			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	08/18/2011	(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 ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 51	Minus	** 51	= 0	X $26 =	0	OR	X $ =	
	Independent (37 CFR 1.16(h))	* 5	Minus	***5	= 0	X $110 =	0	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	0	OR	TOTAL ADD'L FEE	

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)	OR	RATE ($)	ADDITIONAL FEE ($)
	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 number found in the appropriate box in column 1.

Legal Instrument Examiner:
/LAWRENCE BRITT JR/

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.**

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/077,462	03/31/2011	Fabio Trento	23278.20 (US2)

CONFIRMATION NO. 5608

53449
PATENT CORRESPONDENCE
ARNALL GOLDEN GREGORY LLP
171 17TH STREET NW
SUITE 2100
ATLANTA, GA 30363

PUBLICATION NOTICE

OC000000053143251

Title: Compositions and Methods for Treating Centrally Mediated Nausea and Vomiting

Publication No.US-2012-0064153-A1
Publication Date:03/15/2012

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/.

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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

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/077,462	03/31/2011	Fabio Trento	23278.20 (US2)	5608

53449 7590 09/28/2012

PATENT CORRESPONDENCE
ARNALL GOLDEN GREGORY LLP
171 17TH STREET NW
SUITE 2100
ATLANTA, GA 30363

EXAMINER	
WEBB, WALTER E	

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
09/28/2012	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):

patents@agg.com

Office Action Summary	Application No.	Applicant(s)	
	13/077,462	TRENTO ET AL.	
	Examiner	Art Unit	
	WALTER WEBB	1612	

-- 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 *1* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, 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 *31 March 2011*.

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

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

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

Disposition of Claims

5)☒ Claim(s) *1-51* 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) _____ is/are rejected.

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

9)☒ Claim(s) *1-51* are subject to restriction and/or election requirement.

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).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

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

a)☐ All b)☐ Some * c)☐ None of:

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) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-33, 50 and 51, drawn to an oral treatment composition, classified in class 514, subclass 872.

II. Claims 34-49, drawn to an oral treatment composition, classified in class 424, subclass 452.

The inventions are distinct, each from the other because of the following reasons:

Inventions I and II are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. See MPEP § 806.05(h). In the instant case the product as claimed can be used in a method for treating depression.

Restriction for examination purposes as indicated is proper because all these inventions listed in this action are independent or distinct for the reasons given above and there would be a serious search and examination burden if restriction were not required because one or more of the following reasons apply:

(a) the inventions have acquired a separate status in the art in view of their different classification;

(b) the inventions have acquired a separate status in the art due to their recognized divergent subject matter;

(c) the inventions require a different field of search (for example, searching different classes/subclasses or electronic resources, or employing different search queries);

(d) the prior art applicable to one invention would not likely be applicable to another invention;

(e) the inventions are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a invention to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected invention**.

The election of an invention may be made with or without traverse. To reserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected invention.

If claims are added after the election, applicant must indicate which of these claims are readable upon the elected invention.

Should applicant traverse on the ground that the inventions are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Rejoinder Advisory

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and the product claims are subsequently found allowable, withdrawn process claims that depend from or otherwise require all the limitations of the allowable product claim will be considered for rejoinder. All claims directed to a nonelected process invention must require all the limitations of an allowable product claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to

be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product are found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product claim will not be rejoined. See MPEP § 821.04(b). Additionally, in order to retain the right to rejoinder in accordance with the above policy, applicant is advised that the process claims should be amended during prosecution to require the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder**. Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

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-4:00pm Mon-Fri 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

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PATENT CORRESPONDENCE
ARNALL GOLDEN GREGORY LLP
171 17TH STREET NW
SUITE 2100
ATLANTA, GA 30363

Courtesy Reminder for
Application Serial No: 13/077,462

Attorney Docket No: 23278.20 (US2)
Customer Number: 53449
Date of Electronic Notification: 09/28/2012

This is a courtesy reminder that new correspondence is available for this application. The official date of notification of the outgoing correspondence will be indicated on the form PTOL-90 accompanying the correspondence.

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CERTIFICATE OF ELECTRONIC TRANSMISSION UNDER 37 C.F.R. § 1.8

I hereby certify that this correspondence, including any items indicated as attached or included, is being transmitted via electronic transmission via EFS-Web on the date indicated below.

Date: October 30, 2012

/Susan Wray/
Susan Wray

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application: **Fabio TRENTO et al.**	)	Art Unit: **1615**
Application No. **13/077,462**	)	Examiner: **Walter E. Webb**
Filed: **March 31, 2011**	)	Confirmation No.: **5608**
For: **COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING**	)	

AMENDMENT AND RESPONSE TO RESTRICTION REQUIREMENT

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

Arnall Golden Gregory LLP
Customer Number: 53449

Sir:

In response to the Restriction Requirement entered on September 28, 2012, applicant elects for prosecution the claims of Group I (claims 1-33). As the elected species, applicant elects the treatment of CINV for five consecutive days by administering on day one 0.5 mg of palonosetron, 300 mg of netupitant, and 12 mg of dexamethasone, wherein no further netupitant or palonosetron is administered during the five days. Claims 1-33 all read on the elected species.

Applicant makes reference to the article attached in Appendix A by Stathis et al. demonstrating the synergistic behavior of this combination on CINV. This reference was cited in the October 30, 2012, IDS filed by applicant.

Also enclosed herewith is a request for a one-month extension of time and the associated fee (small entity).

CONCLUSION

To the extent any additional fee is owed for this submission, the Commissioner is authorized to charge Deposit Account Number 504667.

Respectfully submitted,

/Clark G. Sullivan/
Clark G. Sullivan
Reg. No. 36,942

Arnall Golden Gregory LLP
171 17th Street NW, Suite 2100
Atlanta, Georgia 30363
404.873.8512 (Direct)
404.873.8513 (Fax)
Customer No.: 53449

AGG Docket: 23278.20

APPENDIX A

European Journal of Pharmacology 689 (2012) 25–30

Contents lists available at SciVerse ScienceDirect

European Journal of Pharmacology

journal homepage: www.elsevier.com/locate/ejphar

Molecular and cellular pharmacology

Inhibition of substance P-mediated responses in NG108-15 cells by netupitant and palonosetron exhibit synergistic effects

Marigo Stathis [a], Claudio Pietra [b], Camilo Rojas [a,*], Barbara S. Slusher [a,**]

[a] Departments of Neurology and Psychiatry (BSS), Brain Science Institute (MS, BSS, CR), Johns Hopkins University School of Medicine, Baltimore Maryland
[b] Helsinn Healthcare (CP), Lugano, Switzerland

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ABSTRACT

Netupitant is a potent and selective NK_1 receptor antagonist under development in combination with a fixed dose of palonosetron for the prevention of chemotherapy induced nausea and vomiting. Palonosetron is a 5-HT_3 receptor antagonist approved for both the prevention of acute and delayed chemotherapy induced nausea and vomiting after moderately emetogenic chemotherapy. Accumulating evidence suggests that substance P (SP), a ligand acting largely on tachykinin (NK_1) receptors, is the dominant mediator of delayed emesis. Interestingly, palonosetron does not bind to the NK_1 receptor so that the mechanism behind palonosetron's unique efficacy against delayed emesis is not clear. Palonosetron exhibits a distinct ability among 5-HT_3 receptor antagonists to inhibit crosstalk between NK_1 and 5-HT_3 receptor signaling pathways. The objective of the current work was to determine if palonosetron's ability to inhibit receptor signaling crosstalk would influence netupitant's inhibition of the SP-mediated response when the two drugs are dosed together. We first studied the inhibition of SP-induced Ca^{2+} mobilization in NG108-15 cells by palonosetron, ondansetron and granisetron. Unexpectedly, in the absence of serotonin, palonosetron inhibited the SP-mediated dose response 15-fold; ondansetron and granisetron had no effect. Netupitant also dose-dependently inhibited the SP response as expected from an NK1 receptor antagonist. Importantly, when both palonosetron and netupitant were present, they exhibited an enhanced inhibition of the SP response compared to either of the two antagonists alone. The results further confirm palonosetron's unique pharmacology among 5-HT_3 receptor antagonists and suggest that it can enhance the prevention of delayed emesis provided by NK_1 receptor antagonists.

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1. Introduction

Current therapy for the treatment of chemotherapy induced nausea and vomiting includes the use of both 5-HT_3 and NK_1 receptor antagonists along with dexamethasone (Basch et al., 2011; Ettinger et al., 2011; Roila et al., 2010). Acute emesis has been largely associated with activation of 5-HT_3 receptors by serotonin while delayed emesis is thought to occur mainly through the activation of NK_1 receptors by substance P (SP) (Hesketh et al., 2003). While treatment of acute emesis was largely resolved with the introduction of 5-HT_3 receptor antagonists in the 1990s, nausea and delayed emesis are lingering problems (Feyer and Jordan, 2011; Oo and Hesketh, 2005). The introduction of NK_1 receptor antagonists has been shown to improve overall antiemetic efficacy including delayed emesis when used along with 5-HT_3 receptor antagonists and dexamethasone (Darmani and Ray, 2009; Feyer and Jordan, 2011; Hesketh et al., 2003). Even though a majority of patients are fully protected against chemotherapy induced nausea and vomiting by the use of these therapies, there are still a significant number of patients that experience nausea and delayed emesis, especially following highly or moderately emetogenic chemotherapies (Feyer and Jordan, 2011). Netupitant is a potent and selective NK_1 receptor antagonist currently under development in combination with a fixed dose of palonosetron for the prevention of chemotherapy induced nausea and vomiting. Palonosetron is the only 5-HT_3 receptor antagonist that has been found to be effective in both acute and delayed chemotherapy induced nausea and vomiting after moderate emetogenic chemotherapy (Aapro et al., 2006; Eisenberg et al., 2003; Gralla et al., 2003; Saito et al., 2009). Since palonosetron does not bind to the NK_1 receptor, the mechanism behind palonosetron's unique efficacy among 5-HT_3 receptor antagonists against nausea and delayed emesis is

* Corresponding author at: Johns Hopkins University Brain Science Institute 855 North Wolfe Street Baltimore, MD 21205 United States. Tel.: +1 410 614 0870; fax: +1 410 614 0659.
** Corresponding author. Tel.: +1 410 614 0662; fax: +1 410 614 0659.
E-mail addresses: crojas2@jhmi.edu (C. Rojas), bslusher@jhmi.edu (B.S. Slusher).

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obscure. Recent mechanism of action studies showed that palonosetron could inhibit SP mediated responses in vitro and in vivo possibly as a result of inhibition of 5-HT_3/NK_1 receptor crosstalk (Rojas et al., 2010b). It is not clear however, if palonosetron's effect on 5-HT_3/NK_1 receptor crosstalk would enhance or negate the inhibition of the SP response when used in combination with NK_1 antagonists. In the present work, we used NG108-15 cells known to express both the 5-HT_3 and NK_1 receptors (Emerit et al., 1993; Reiser and Hamprecht, 1989), to study the inhibition of the SP response by netupitant and palonosetron. We report that netupitant and palonosetron exhibit a synergistic effect in the prevention of the SP-mediated response in these cells.

2. Materials and methods

2.1. Calcium-ion release measurements in NG108-15 cells

NG108-15 cells were grown to 95% confluence in high-glucose Dulbecco's modified Eagle's medium. Medium was supplemented with a mixture of sodium hypoxanthine, aminopterin, and thymidine, 10% heat-inactivated fetal bovine serum, glutamine (2 mM), penicillin (100 units), streptomycin (100 μg), and amphotericin B (0.25 μg). All media exchanges were preceded by a 2–5 min plate spin at 168 × *g*, to prevent loosely adherent cells from coming off the plate surface. When determining the effect of 5-HT_3 receptor antagonists on the SP response, cells were pre-incubated for 1 h at 37 °C with either growth media alone (control) or media containing palonosetron (6 nM), ondansetron (300 nM) and granisetron (50 nM). Antagonist concentrations were at least 30-fold the K_d value to ensure receptor saturation (Rojas et al., 2010b). After preincubation, antagonists were removed and cells were rinsed with growth media alone for an additional hour to allow for dissociation of antagonists still bound to receptor. Cell media were then replaced with isosmotic HEPES buffer (pH 7.4, 20 mM) containing NaCl (130 mM), KCl (2 mM), $MgCl_2$ (1 mM) $CaCl_2$ (2 mM), Fluo-4 acetoxymethyl (AM) ester (2 μM), pluronic acid (0.04%) and SP at various concentrations in the 3 nM to 1 mM range. The final incubation lasted for 1 h at 37 °C. Pluronic acid was added as a nonionic surfactant to sequester the AM ester molecules into micelles for cellular uptake. Calcium-ion release was measured for 3 min using a fluorimetric imaging plate reader (FLIPR 1 system), utilizing a Detector Controller (Princeton Instruments, Inc.) and a Sapphire CDRH-HP air-cooled laser at 250 mW, 488 nm excitation (Coherent Inc., Santa Clara, CA).

Experimental protocol was the same when determining the response to change of concentration of netupitant, palonosetron, or netupitant plus palonosetron; in this case, various concentrations of antagonist(s) were used during preincubation. Similarly, SP was replaced by [Sar^9, $Met(O_2)^{11}$] Sub-P, GR-64349, or Senktide (0.6–200 μM) when determining the effects of selective NK_1, NK_2 and NK_3 agonists respectively.

2.2. Statistical analysis

FLIPR Control Software for Windows NT (Version 1.13, Molecular Devices Inc., Sunnyvale, CA) was employed to record the measurements. The max–min signal values generated between 12 and 150 s were subsequently analyzed. Data were normalized to SP control values for baseline and maximal response and a nonlinear regression variable slope analysis using Prism (GraphPad Software Inc, San Diego, CA) was used to obtain EC_{50} values of normalized response vs. log of inhibitor concentration. Error bars correspond to standard error of the mean (S.E.M.).

3. Results

3.1. Palonosetron inhibited the SP response in the absence of serotonin

When cells were preincubated with a saturating concentration of palonosetron (6 nM) in the absence of serotonin followed by media changes to remove antagonist remaining on the cell surface, the SP-induced response was significantly inhibited. The SP response after preincubation with palonosetron exhibited an EC_{50} of 30 ± 6 μM which corresponded to a 15-fold shift to the right compared to the SP response in control cells i.e., when there was no preincubation with palonosetron (EC_{50} = 2 ± 0.2 μM) (Fig. 1). In contrast, the SP response was not affected by preincubation with saturating concentrations of granisetron (50 nM) or ondansetron (300 nM) (Fig. 1).

3.2. Inhibition of SP response by netupitant and palonosetron is synergistic

In order to study the effect of palonosetron on the inhibition of the SP response by an NK_1 receptor antagonist (netupitant), we first determined the effect of each individual agent separately on the SP response at various concentrations. The EC_{50} of the SP response was not changed by netupitant at 1 nM, it gradually shifted to the right at 3 and 10 nM and there was maximal inhibition at 30 nM (Table 1 and Fig. 2A). Similarly, palonosetron exhibited a threshold concentration (0.2 nM) at which there was no effect on the SP response. Palonosetron increasingly inhibited the SP response at 0.6 and 2 nM and had maximal inhibitory effect at 6 nM (Table 1 and Fig. 2B).

We then determined the effect on the SP response when both palonosetron and netupitant were present at threshold concentrations, i.e., concentrations at which neither antagonist inhibited the SP response: netupitant at 1 nM and palonosetron at 0.2 nM. When both antagonists were present at threshold concentrations there was an approximately 60-fold shift in EC_{50} of the SP response when compared to the EC_{50} in the presence of each antagonist alone (Table 1, Fig. 2C).

In the next set of experiments, we determined the effect on the SP response when both palonosetron and netupitant were present

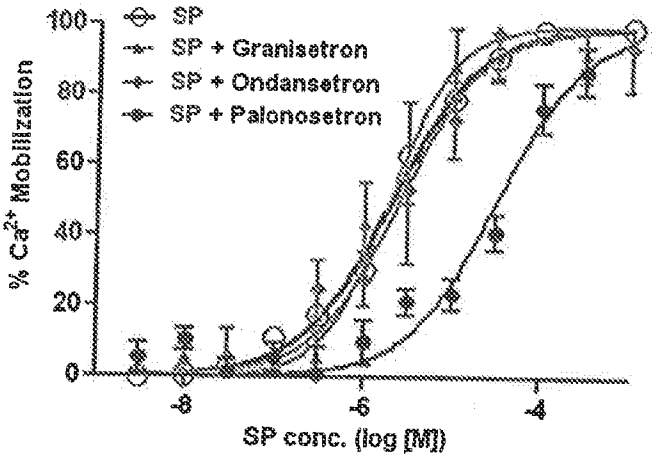


Fig. 1. Effect of 5-HT_3 receptor antagonists on SP induced calcium-ion mobilization in NG108-15 cells. Cells were pre-incubated with saturating concentrations (≥30-fold K_d) of granisetron (50 nM), ondansetron (300 nM) or palonosetron (10 nM) for 1 h at 37 °C. Subsequent to complete removal of antagonists, the cells were incubated with SP at different concentrations before measurement of calcium-ion mobilization (Materials and Methods). EC_{50} values for SP (n = 38), SP + ondansetron (n = 4) and SP + granisetron (n = 3) were all 3 μM. EC_{50} value for SP + palonosetron was 30 ± 6 μM (n = 5). Error bars correspond to ± S.E.M.

Table 1
Inhibition of SP response in NG108-15 cells by netupitant (netu) and palonosetron (palo).

SP + Antagonist(s)	EC_{50} (μM) ± S.E.M.	n
SP only	2 ± 0.2	38
Plus netu (1 nM)	2 ± 0.3	3
Plus netu (3 nM)	5 ± 3	3
Plus netu (10 nM)	10 ± 0.9	3
Plus netu (30 nM)	40 ± 10[a]	6
Plus palo (0.2 nM)	2 ± 0.1	3
Plus palo (0.6 nM)	3 ± 0.6	3
Plus palo (2 nM)	10 ± 2	3
Plus palo (6 nM)	30 ± 6[a]	5
Plus net (1 nM) plus palo (0.2 nM)	120 ± 20[b]	7
Plus net (30 nM) plus palo (6 nM)	970 ± 150[c]	5

Cells were pre-incubated with netupitant, palonosetron or combinations of palonosetron plus netupitant at various concentrations as indicated for 1 h at 37 °C. After antagonist(s) removal, cells were incubated at 37 °C for 1 h with various SP concentrations, followed by measurement of calcium-ion mobilization. SP only had $n=38$ because it was used as control in all experiments. When using antagonists, data were the average of $n=3-7$ determinations as indicated. GraphPad Prism was used to obtain EC_{50} values (Materials and Methods). The traces with the experimental points that generated the EC_{50} values are given in Fig. 2.

[a] $P<0.001$ compared to SP only.
[b] $P<0.05$ compared to netupitant alone at 1 nM or palo alone at 0.2 nM.
[c] $P<0.001$ compared to netupitant alone at 30 nM or to palo alone at 6 nM.

at concentrations where maximal inhibition was observed with each antagonist: netupitant at 30 nM and palonosetron at 6 nM. The EC_{50} of the dose response under these conditions was 970 ± 150 μM, representing a 22-fold shift with respect to maximal inhibition by netupitant ($P<0.001$) and a 30-fold shift with respect to maximal inhibition by palonosetron ($P<0.001$) (Table 1, Fig. 2D). In cases where maximal activity was not reached even at 1 mM SP, the EC_{50}s represent the concentration of SP required to obtain 50% of the control response rather than 50% of maximal activity. There was a decrease in the maximum response when both palonosetron and netupitant were used (R_{max}) suggesting that fewer receptors became available. The results showed a synergistic effect on the inhibition of the SP response both when palonosetron and netupitant were present at threshold and when using maximal inhibitory concentrations.

3.3. *Inhibition of the SP-response by netupitant and palonosetron occurs selectively through inhibition of the NK_1 receptor signaling pathway*

Experiments with selective NK_1 ([Sar^9, $Met(O_2)^{11}$]-Substance P), NK_2 (GR 64349) and NK_3 (Senktide) receptor agonists exhibited calcium-ion mobilization in a dose-response manner indicating that these three receptors are found in NG108-15 cells.

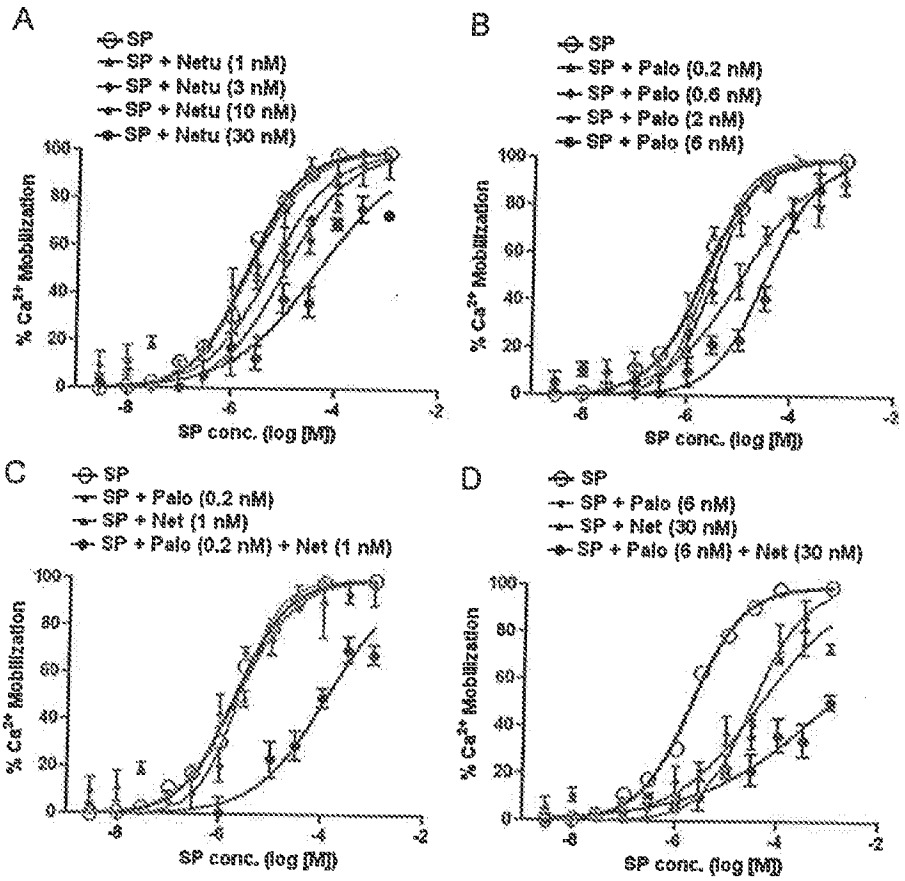


Fig. 2. Effect on SP response in NG108-15 cells when using palonosetron alone, netupitant alone and palonosetron plus netupitant. Cells were pre-incubated with netupitant, palonosetron or a combination of palonosetron plus netupitant. After antagonist(s) removal, cells were incubated at 37 °C for 1 h with various SP concentrations, followed by measurement of calcium-ion mobilization. (A) Netupitant alone. (B) Palonosetron alone. (C) Threshold concentrations of netupitant (1 nM) and palonosetron (0.2 nM) alone and in combination. Threshold concentrations were concentrations at which no inhibition of the SP response was observed when each antagonist was used alone. (D) Maximal concentrations of netupitant (30 nM) and palonosetron (6 nM) alone and in combination. Maximal concentrations were concentrations at which maximal inhibition of the SP response was observed when each antagonist was used alone. EC_{50}s and n values for each trace are listed in Table 1 In cases where maximal activity was not reached even at an SP concentration of 1 mM, the EC_{50}s represent the SP concentration required to obtain 50% of the control response rather than 50% of maximal activity. Error bars correspond to ± S.E.M.

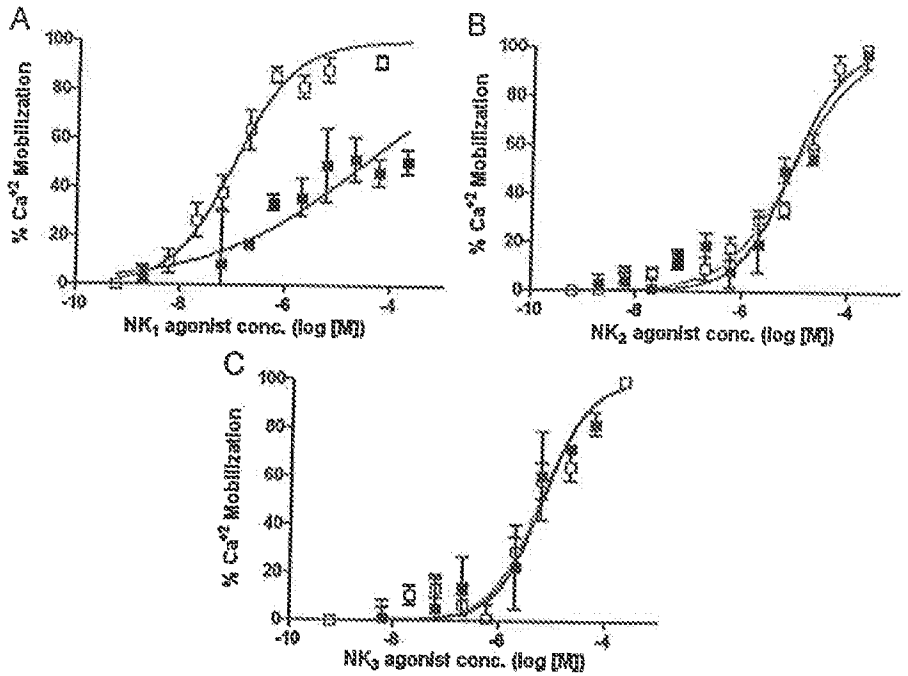


Fig. 3. Effect of palonosetron and netupitant on selective NK_1, NK_2 and NK_3 agonist -induced calcium-ion mobilization in NG108-15 cells. NG108-15 cells were pre-incubated with netupitant (30 nM) and palonosetron (6 nM) for 1 h at 37 °C. Parallel incubations without antagonist were used as controls. After removal of palonosetron and netupitant, cells were incubated at 37 °C for 1 h with various concentrations of selective agonists to NK receptors before measurement of calcium-ion mobilization. (A) Empty squares and gray trace: response to selective NK_1 agonist ([Sar^9, Met $(O_2)^{11}$]—Substance P); EC_{50}=0.1 ± 0.03 μM (n=7). Filled squares and black trace: response to NK_1 agonist plus netupitant and palonosetron; EC_{50}=30 ± 15 μM (n=3). (B) Empty squares and gray trace: response to selective NK_2 agonist (GR 64349); EC_{50}=8 ± 2 μM (n=9). Filled squares and black trace: response to NK_2 agonist plus netupitant and palonosetron; EC_{50}=8 ± 2 μM (n=4). (C) Empty squares and gray trace: response to selective NK_3 agonist (Senktide); EC_{50}=6 ± 1 μM (n=9). Filled squares and black trace: response to NK_3 agonist plus netupitant and palonosetron; EC_{50}=6 ± 4 μM (n=3). Error bars correspond to ± S.E.M.

Palonosetron and netupitant significantly inhibited the selective NK_1 receptor agonist effect on calcium-ion mobilization; the EC_{50} shifted to the right approximately 300-fold from 0.1 ± 0.03 μM when using [Sar^9, Met $(O_2)^{11}$]—Sub-P to 30 ± 15 μM when using [Sar^9, Met $(O_2)^{11}$]—Sub-P plus netupitant and palonosetron (Fig. 3A). In contrast, netupitant plus palonosetron did not inhibit the selective NK_2 or NK_3 receptor agonist-induced calcium-ion mobilization (Fig. 3B and C).

4. Discussion

Recent studies showed that palonosetron inhibits SP mediated responses in vitro and in vivo possibly as a result of inhibition of 5-HT_3/NK_1 receptor crosstalk. Specifically, palonosetron was found to inhibit the serotonin enhancement of the SP response in NG108-15 cells and the cisplatin enhancement of the neuronal response to SP in rat nodose ganglia. This inhibition was not observed when using ondansetron or granisetron, two other commonly used 5-HT_3 receptor antagonists (Rojas et al., 2010b). These results helped provide a rationale for palonosetron's unique ability among 5-HT_3 receptor antagonists to prevent nausea and delayed emesis after moderate emetogenic chemotherapy. Given the inhibition of delayed emesis by NK_1 receptor antagonists, it is not clear if palonosetron's inhibition would make any difference if co-administered with an NK_1 receptor antagonist. In order to address this question, we studied the inhibition of SP-induced calcium-ion mobilization in NG108-15 cells by palonosetron and netupitant, a selective NK_1 receptor antagonist.

During preliminary experiments with 5-HT_3 receptor antagonists, preincubation of NG108-15 cells with a saturating concentration of palonosetron in the absence of serotonin significantly inhibited the SP response. In contrast, the SP response was not affected by preincubation of cells with saturating concentrations of either granisetron or ondansetron (Fig. 1). The results showed that we could differentiate palonosetron's inhibition of SP-induced calcium-ion mobilization from its inhibition of serotonin-induced calcium-ion mobilization when using these cells. The results also suggested that palonosetron's ability to trigger 5-HT_3 receptor internalization and subsequently inhibit SP-induced responses can occur even in the absence of serotonin. The mechanism by which palonosetron inhibits NK_1 signaling is unclear. It is possible that palonosetron-induced 5-HT_3 receptor internalization causes a down regulation of second messenger systems which limits NK_1 signaling. Alternatively, the internalization of the 5-HT_3 receptor could lead to subsequent partial internalization of the NK_1 receptor. A case of a ligand binding to one receptor and triggering internalization of another receptor has been reported recently: NMDA binding to the NMDA receptor triggers internalization of the $GABA_B$ receptor. (Guetg et al., 2010). It is noteworthy that palonosetron did not completely eliminate NK_1 receptor signaling (Fig. 1); this is in accord with clinical data showing that palonosetron's antiemetic efficacy can be enhanced when dosed with an NK_1 receptor antagonist (Longo et al., 2010; Schwartzberg et al., 2011). Another possibility is that the receptor–palonosetron complex could be targeted for receptor degradation rather than recycling to the cell surface with a concomitant disturbance of downstream 5-HT_3/NK_1 signaling interactions. Relevant to this possibility, 5-HT_3 receptor replenishment at the cell surface after palonosetron-triggered internalization does not occur within the first 2.5 h of exposure to the antagonist (Rojas et al., 2010a), whereas 5-HT_3 receptors reappear at the surface 1 h after serotonin-induced internalization (Freeman et al., 2006; Rojas et al., 2010a). Second messenger

systems that are activated following NK_1 receptor signaling could also be inhibited after exposure of cells to palonosetron. In addition to calcium-ion mobilization, stimulation of phosphoinositol turnover, arachidonic acid mobilization, and cyclic AMP accumulation have all been associated with the NK_1 receptor response (Quartara and Maggi, 1997). The details of palonosetron's effects on NK_1 receptor trafficking as well as effects on second messenger systems are the subject of current investigations in our laboratory. Regardless of the selective mechanism however, the ability to discriminate palonosetron's inhibition of the SP versus serotonin response provided a springboard to carry out experiments to determine if palonosetron's inhibition of the SP response could alter the effect of NK_1 receptor antagonists.

We proceeded to determine the separate effect of palonosetron and of an NK_1 receptor antagonist (netupitant) on the SP response at various concentrations. We decided to use the combination of palonosetron and netupitant because this $5HT_3$/NK_1 receptor antagonist antiemetic combination is currently in clinical development. Netupitant did not inhibit the SP response at 1 nM; it increasingly inhibited the SP response at 3 and 10 nM and exhibited maximal inhibition at 30 nM (Table 1 and Fig. 2A). Similarly, palonosetron did not inhibit the SP response at 0.2 nM; it showed increasing inhibition at 0.6 and 2 nM and exhibited maximal inhibition of the SP response at 6 nM (Table 1, Fig. 2B).

These results provided the information on the concentrations to use in the subsequent set of experiments when both the antagonists were used in combination. We first determined the effect on SP response when both palonosetron and netupitant were present at threshold concentrations, i.e., concentrations at which neither antagonist inhibited the SP response: netupitant at 1 nM and palonosetron at 0.2 nM. In this case there was an approximately 60-fold shift in EC_{50} of the SP response when compared to the EC_{50} in the presence of each antagonist alone (Table 1, Fig. 2C). We then determined the effect on the SP response when both palonosetron and netupitant were present at concentrations where maximal inhibition was observed with each antagonist: netupitant at 30 nM and palonosetron at 6 nM. Under these conditions, the EC_{50} represented a 22-fold shift to the right with respect to maximal inhibition by netupitant ($P<0.001$) and a 30-fold increase in EC_{50} with respect to maximal inhibition by palonosetron ($P<0.001$) (Table 1, Fig. 2D). The maximum response when using palonosetron plus netupitant was not reached; this is the hallmark of lower receptor availability, a finding consistent with NK_1 receptor internalization. The results showed a synergistic effect on the inhibition of the SP response regardless of whether palonosetron and netupitant were present at threshold or maximal inhibitory concentrations. Synergistic activity between drugs in other systems has been reported previously. For example, addition of the protein tyrosine kinase inhibitor genistein has been shown to synergistically increase the antiproliferative effect of camptothecins in a variety of cell lines (Papazisis et al., 2006). In another study, when combined with inactive doses of 5-fluorouracil (5-FU), the antiangiogenic drug rapamycin significantly improved outcomes in a murine colon adenocarcinoma model as compared to rapamycin dosing alone (Seeliger et al., 2004). Systematic screening for synergistic drug combinations has also been the subject of recent investigations (Borisy et al., 2003; Li et al., 2011).

Receptor cross-talk can be defined as the activation of one receptor by its ligand that in turn influences the cellular responses to another receptor system. Crosstalk between the $5\text{-}HT_3$ and NK_1 receptor signaling systems has been demonstrated by several independent laboratories. For example, $5\text{-}HT_3$ receptor antagonists have been shown to block SP-mediated vagal afferent activation (Minami et al., 2001). In addition, NK_1 antagonism can block serotonin-induced vagal afferent activation (Minami et al., 2001). In separate studies, SP, an agonist at the NK_1 receptor, was shown to potentiate $5\text{-}HT_3$ receptor mediated current in rat trigeminal ganglion neurons (Hu et al., 2004). In another set of studies, palonosetron, an antagonist of the $5\text{-}HT_3$ receptor, was shown to inhibit the serotonin enhancement of the SP response in NG108-15 cells and the cisplatin enhancement of the neuronal response to SP in rat nodose ganglia (Rojas et al., 2010b). Consequently, the potential inhibition of downstream receptor crosstalk, in addition to direct receptor antagonism, represents an additional layer of inhibition that could trigger synergistic inhibitory effects. Recent studies have reported synergistic antiemetic interactions brought about by a combination of tropisetron, a $5\text{-}HT_3$ antagonist and CP 99994 an NK_1 receptor antagonist against vomiting in the least shrew (Darmani et al., 2011). However, synergism against emesis in this case was observed only at a small dose range due to tropisetron's ability to act as partial agonist at higher concentrations.

Given the relevance of the NK_1 receptor to emesis, we wanted to rule out the possibility that the SP effects on calcium-ion mobilization and the corresponding inhibition by palonosetron and netupitant observed in these cells were not occurring through other NK receptors. Experiments with selective NK_1 and NK_2 selective receptor agonists exhibited calcium-ion mobilization in a dose-response manner indicating that these three receptors are found in NG108-15 cells. Consequently, it was possible that these receptors and their signaling could be at least partially responsible for the observed inhibition. In order to rule out this possibility, we looked to see if palonosetron and netupitant could inhibit the effect of these selective NK receptor agonists. Palonosetron plus netupitant significantly inhibited the selective NK_1 receptor agonist effect on calcium-ion mobilization; EC_{50} shifted to the right approximately 300-fold (Fig. 3A). In contrast, palonosetron plus netupitant did not inhibit the selective NK_2 or NK_3 receptor agonist-induced calcium-ion mobilization (Fig. 3B and C). The results indicated that inhibition of calcium-ion mobilization by palonosetron and netupitant in these cells must be occurring through the NK_1 receptor.

It is important to point out that these studies use NG108-15 cells as a model of the potential mechanism of action on delayed emesis when using palonosetron and netupitant in humans. Clearly, NG108-15 cells do not incorporate the complexities of a whole organism and the results obtained in these studies are only a first approximation of what could be observed in the clinic.

In summary, the results suggest that not all $5\text{-}HT_3$ receptor antagonists are the same. Palonosetron, but not ondansetron or granisetron could inhibit the SP response in NG108-15 cells in the absence of serotonin. Further, inhibition by palonosetron and NK_1 antagonists of the SP response in NG108-15 cells is synergistic. This inhibition is selective to the NK_1 receptor and its crosstalk with the $5\text{-}HT_3$ receptor signaling system. $5\text{-}HT_3$ antagonists that inhibit $5\text{-}HT_3$/NK_1 receptor signaling crosstalk in addition to antagonizing the $5\text{-}HT_3$ receptor could bring about an enhanced antiemetic effect during nausea and delayed emesis. The results support the use of the combination of palonosetron and NK-1 receptor antagonists in the prevention of chemotherapy induced nausea and vomiting.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application:	**Fabio TRENTO et al.**	Art Unit:	**1615**
Application No.	**13/077,462**	Examiner:	**Walter E. Webb**
Filed:	**March 31, 2011**	Confirmation No.:	**5608**
For:	**COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING**		

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It is respectfully requested that an extension of time for the period indicated below be granted in accordance with the provisions of 37 C.F.R. Section 1.136 to take action required in the application identified in the caption, as reflected by the papers submitted herewith:

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the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment, to Deposit Account No. 50-4667.

Respectfully submitted,

/Clark G. Sullivan/
Clark G. Sullivan
Reg. No. 36,942

Arnall Golden Gregory LLP
171 17th Street NW, Suite 2100
Atlanta, Georgia 30363
404.873.8512 (Direct)
404.873.8513 (Fax)
Customer No.: 53449

AGG Docket: 23278.20

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	13077462
Filing Date	2011-03-31
First Named Inventor	Trento, Fabio
Art Unit	1612
Examiner Name	Webb, Walter E.
Attorney Docket Number	23278.20

U.S.PATENTS

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, III et al.	
	3	6297375		2001-10-02	Bös et al.	
	4	6719996		2004-04-13	Kuentz et al.	
	5	6593472		2003-07-15	Hoffmann et al.	

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FOREIGN PATENT DOCUMENTS

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
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	Attorney Docket Number	23278.20

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	WO 2008/049552 A1			2008-05-02	Helsinn Healthcare SA		☐
	2	WO 2004/067005 A1			2004-08-12	Helsinn Healthcare SA		☐
	3	WO 2004/073714 A1			2004-09-02	Helsinn Healthcare SA		☐
	4	WO 2004/045615 A1			2004-06-03	Helsinn Healthcare SA		☐

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NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	March 27, 2003, Approved FDA Prescribing Information for Emend	☐
	2	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	☐
	3	PELLEGATTI, MARIO et al., "Disposition and Metabolism of Radiolabeled Casopitant in Humans," Drug Metabolism and Disposition, vol. 37, no. 8, 2009, pp.1635-1645	☐
	4	HUANG, SHIH-CHUNG et al., "Neurokinin-1 receptor antagonists: a comprehensive patent survey," Expert Opin. Ther. Patents (2010) 20(8), pp. 1019-1045	☐

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	Filing Date	2011-03-31
	First Named Inventor	Trento, Fabio
	Art Unit	1612
	Examiner Name	Webb, Walter E.
	Attorney Docket Number	23278.20

	5	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	☐
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	9	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	☐
	10	STATHIS, MARIGO et al., "Inhibition of substance P-mediated responses in NG108-15 cells by netupitant and palonosetron exhibit synergistic effects," European Journal of Pharmacology 689 (2012) pp. 25-30	☐

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	Art Unit	1612
	Examiner Name	Webb, Walter E.
	Attorney Docket Number	23278.20

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

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☐ 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)	2012-10-30
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.**

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(71) Applicant *(for all designated States except US)*: **HELSINN HEALTHCARE S.A.** [CH/CH]; P.O. Box 357, CH-6915 Lugano/Pambio-Noranco (CH).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **BONADEO, Daniele** [IT/IT]; Via Ronco Capo Caccia, 32, I-21030 Casalzuigno, Varese (IT). **CALDERARI, Giorgio** [CH/CH]; Via Scer, CH-6862 Rancate (CH). **BRAGLIA, Enrico** [CH/CH]; Via Pian Scairolo, 9, CH-6912 Lugano-Pazzallo (CH). **BRAGLIA, Riccardo** [CH/CH]; Via Pian Scairolo, 9, CH-6912 Lugano-Pazzallo (CH).

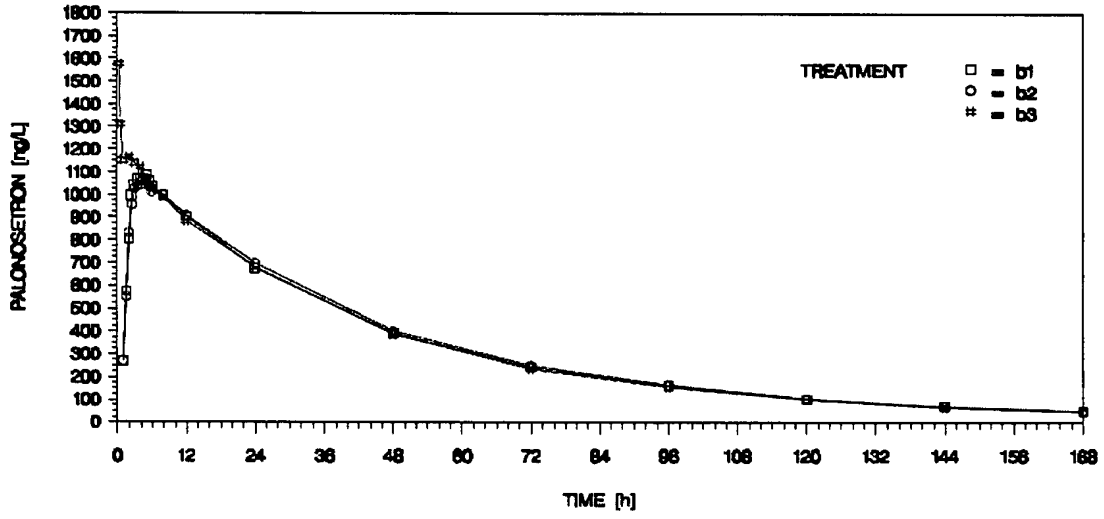
(74) Agent: **LEISSLER-GERSTL, Gabriele**; Hoefer & Partner, Pilgersheimer Strasse 20, 81543 München (DE).

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(54) **Title:** SOFT CAPSULES COMPRISING PALONOSETRON HYDROCHLORIDE HAVING IMPROVED STABILITY AND BIOAVAILABILITY



(57) **Abstract:** Provided are solid oral dosage forms of palonosetron hydrochloride, methods of using the dosage forms to treat emesis, and methods of making the dosage forms. The dosage forms have improved stability and bioavailability, and are preferably in the form of liquid filled capsules.

WO 2008/049552 A1

SOFT CAPSULES COMPRISING PALONOSETRON HYDROCHLORIDE HAVING IMPROVED STABILITY AND BIOAVAILABILITY

RELATIONSHIP TO PRIOR APPLICATIONS

The present application claims priority to United States Provisional Application No. 60/854,342, filed October 24, 2006 (expired).

FIELD OF THE INVENTION

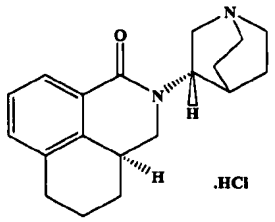
The present invention relates to palonosetron, and especially to solid oral dosage forms of palonosetron hydrochloride that meet demanding shelf stability requirements.

BACKGROUND OF THE INVENTION

The nausea and emetogenic side effects of anti-cancer chemotherapy and radiotherapy are a widespread and longstanding problem. Perhaps less well known but no less important are post-operative nausea and emesis, which may have physiological mechanisms related to the effects seen for chemotherapy. Palonosetron hydrochloride has recently emerged as a highly efficacious anti-nauseant and anti-emetic for use with emetogenic anti-cancer chemotherapies. (Macciocchi, A., *et al.*, "A Phase II dose-ranging study to assesses single intravenous doses of palonosetron for the prevention of highly emetogenic chemotherapy-induced nausea and vomiting," *Proc. Am. Soc. Clin. Oncol.*, 2002; Abstract 1480. Palonosetron also prevents postoperative nausea and vomiting. (Chelly, J., *et al.*, "Oral RS-25259 prevents postoperative nausea and vomiting following laparoscopic surgery," *Anesthesiol.*, 85(Suppl. 21):abstract no. 3A (1996)). Methods of treating chemotherapy induced nausea and vomiting (CINV) and radiation induced nausea and vomiting (RINV) with palonosetron are described in PCT publication WO 2004/045615 from Helsinn Healthcare SA. Methods of treating post-operative nausea and vomiting (PONV) with palonosetron are described in PCT publication 2004/073714, also from Helsinn Healthcare SA.

Palonosetron is selective, showing a high affinity as an antagonist for the 5-hydroxyltryptamine 3 receptor precursor (5-HT_3 receptor), and showing a low affinity for other receptors such as dopamine receptors (Wong, E.H.F., *et al.*, "The interaction of RS 25259-197, a potent and selective antagonist, with 5-HT_3 receptors, in vitro," *Br. J. Pharmacol.*, 114:851-859

(1995); Eglen, R.M., *et al.*, "Pharmacological characterization of RS 25259-197, a potent and selective antagonist, with 5-HT_3 receptors, in vivo," *Br. J. Pharmacol.*, 114:860-866 (1995)). Palonosetron is a synthetic compound existing as a single isomer, and is administered as the hydrochloride salt, as represented in the following structure:



The official chemical name for the drug is (3aS)-2-[(S)-1-Azabicyclo [2.2.2]oct-3-yl]-2,3,3a,4,5,6-hexahydro-1-oxo-1*H*benz[*de*] isoquinoline hydrochloride (CAS No. 119904-90-4); its empirical formula is $C_{19}H_{24}N_2O$•HCl, and its molecular weight is 332.87. Methods of synthesizing the compound are described in U.S. Patent Nos. 5,202,333 and 5,510,486.

Palonosetron hydrochloride is sold as a sterile injectable liquid in the United States as ALOXI® by MGI Pharma and Helsinn Healthcare SA. The intravenous liquid is clear, colorless, non-pyrogenic, in an isotonic, buffered solution. A stable isotonic solution of palonosetron for injection is described in Helsinn's PCT publication WO 2004/067005.

Despite the numerous clinical benefits and advantages of this intravenous formulation, it is generally recognized that injection drug delivery systems present special problems with respect to storage life and stability of the active agent. They are also inconvenient when self administered, and have increased risk of contamination and human error. Thus an oral delivery option for palonosetron, especially in solid form, would be particularly attractive. Methods for improving the stability and shelf-life of palonosetron formulations would also be desirable.

SUMMARY OF THE INVENTION

Soft-gel capsules of palonosetron have been developed that exhibit excellent bioavailability when orally ingested, and stability when stored for prolonged periods of time. The outer shell for the capsule is gelatin based, and the inner fill for the capsule is a continuous lipophilic inner phase that contains palonosetron dissolved in an aqueous component, miscibilized or homogenized in the lipophilic phase by minimal quantities of a surfactant. The formulation represents an elegant solution to the tension commonly observed between:

- aqueous fills and gelatin stability;
- surfactant and palonosetron degradation; and
- palonosetron stability and palonosetron concentration

In a first principal embodiment, therefore, the invention provides a soft gelatin capsule for oral administration comprising: (a) a soft gelatin outer shell having an oxygen permeability of less than about 1.0×10^{-3} ml·cm/(cm^2·24 hr. atm); and (b) a lipophilic liquid inner fill composition comprising: (i) greater than about 50 wt.% of one or more lipophilic components; (ii) from about 1 to about 20 wt.% of water miscibilized or homogenized in said one or more lipophilic components; (iii) from about 0.05 to about 2.0 mg. of palonosetron as palonosetron hydrochloride solubilized or dispersed in said water; and (iv) from about 0.5 to about 5 wt.% of a surfactant.

Formulations and methods of manufacture have also been developed that can be defined by the amount or concentration of palonosetron in the dosage form, and the degradation byproducts within the dosage form. One such degradation by product is an oxygen mediated degradation product, and is referred to herein as "Cpd1."

Dosage forms of palonosetron, including methods of manufacture, have also been developed with enhanced stability due to their protection from oxygen and oxygen mediated degradation. Based on these discoveries and developments, dosage forms have been developed that can be defined by one or more of the following physical features:

- a shell or coating that is substantially impermeable to oxygen;
- the use of a liquid filling within a capsule shell, preferably containing water;
- a minimal oxygen content in the liquid filling;
- chemical means for preventing oxidative degradation;
- moisture resistant packaging that is resistant to oxygen permeation; and/or
- use of an oxygen-depleted environment while manufacturing the dosage form.

These dosage forms have excellent stability over prolonged periods of time, excellent resistance to oxidative degradation, and excellent bioavailability when orally ingested. These dosage forms can be used in the treatment of any disease for which palonosetron has clinical utility, but they are preferably used for the treatment of emesis.

In a second principal embodiment, therefore, the invention provides a capsule dosage form for oral administration comprising: (a) an outer shell having a oxygen permeability of less than about 1.0×10^{-3} ml·cm/(cm^2·24 hr. atm); and (b) an inner fill composition comprising: from about 0.05 to about 2.0 mg. of palonosetron as palonosetron hydrochloride, wherein said palonosetron comprises Cpd1 in an amount of less than 1.0 wt.%; wherein no more than 5.0 wt.% of said palonosetron hydrochloride degrades when said dosage form is stored three months or greater at 40 °C and 75% RH.

Of course, the invention could be practiced using dosage forms other than capsules, and in another embodiment the invention provides a solid oral dosage form comprising: (a) an outer shell or coating having a oxygen permeability of less than about 1.0×10^{-3} ml·cm/(cm^2·24 hr. atm); and (b) an inner fill composition comprising: from about 0.05 to about 2.0 mg. of palonosetron as palonosetron hydrochloride, wherein said palonosetron comprises Cpd1 in an amount of less than 1.0 wt.%; wherein no more than 5.0 wt.% of said palonosetron hydrochloride degrades when said dosage form is stored three months or greater at 40 °C and 75% RH.

Methods have also been developed for manufacturing palonosetron dosage forms that have reduced quantities of impurities and oxygen mediated degradation products, and to palonosetron dosage forms manufactured by these methods. Thus, in still another embodiment the invention provides a method for manufacturing a batch of palonosetron dosage forms having reduced quantities of impurities and oxygen mediated degradation products comprising (a) mixing palonosetron hydrochloride and one or more pharmaceutically acceptable excipients to form a mixture; (b) processing said mixture into a plurality of final dosage forms; and (c) testing one or more of said final dosage forms for Cpd1. This method can be practiced with any dosage form, including a capsule, gel-cap or liquid filled ampoule.

Additional 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 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.

IN THE FIGURES

Figure 1 plots pharmacokinetics observed in human patients from a bioequivalence study, wherein b1 represents treatment by clinical Formulation A, b2 represents treatment by commercial Formulation B, and b3 represented treatment by Aloxi® i.v.

Figure 2 plots pharmacokinetics observed in human patients from a bioequivalence study, wherein b1 represents clinical formulation A, and b2 represents commercial formulation B.

Both figures report arithmetic mean plasma concentrations of palonosetron (ng/ml) versus time (H) on a linear scale (n=33).

DETAILED DESCRIPTION OF THE INVENTION

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

Definitions and Use of Terms

As used in this specification and in the claims which follow, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "an ingredient" includes mixtures of ingredients, reference to "an active pharmaceutical agent" includes more than one active pharmaceutical agent, and the like.

"Treating" or "treatment" of a disease includes (1) preventing the disease from occurring in an animal that may be predisposed to the disease but does not yet experience or display symptoms of the disease, (2) inhibiting the disease, i.e. arresting its development, or (3) relieving the disease, i.e. causing regression of the disease.

As used herein, an ambient environment refers to the environment immediately surrounding an element or process, typically a gaseous environment, with which the element or process is in contact and communication.

"Emesis," for the purposes of this application, will have a meaning that is broader than the normal, dictionary definition and includes not only vomiting, but also nausea and retching.

"Moderately emetogenic chemotherapy" refers to chemotherapy in which the emetogenic potential is comparable or equivalent to the emetogenic potential of carboplatin, cisplatin $\leq$ 50 mg/m^2, cyclophosphamide < 1500 mg/m^2, doxorubicin > 25 mg/ms, epirubicin, irinotecan, or methotrexate > 250 mg/m^2.

"Highly emetogenic chemotherapy" refers to chemotherapy in which the emetogenic potential is comparable or equivalent to the emetogenic potential of cisplatin $\geq$ 60 mg/m^2, cyclophosphamide > 1500 mg/m^2, or dacarbazine.

"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.

"Therapeutically effective amount" means that amount which, when administered to an animal for treating a disease, is sufficient to effect such treatment for the disease.

A "de minimis" quantity of oxygen refers to an amount of oxygen that allows no more than about 0.5, 1.0, 1.5, 2.0, 2.5, or 3.0 wt.% of said palonosetron to degrade (preferably defined by degradation to Cpd1) when stored at room temperature under ambient conditions for six, twelve, eighteen, twenty-four, thirty or thirty-six months.

Shelf stability, for purposes of this invention, is measured by storing the dosage form in its packaging at 40 °C, at a relative humidity of 75%, or under ambient conditions, for three, six, twelve, eighteen, twenty-four, thirty or thirty-six months. A stable formulation is one in which no more than about 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, or 5.0 wt.% of the palonosetron in the dosage form degrades (preferably defined by degradation to one or more of the degradation products described herein).

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.

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 due to manufacturing variation 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 bioequivalent to the recited strength of a claimed product.

The term "absolute bioavailability" refers to the availability of the active drug in systemic circulation after non-intravenous administration (i.e., after oral, rectal, transdermal, subcutaneous administration). In order to determine absolute bioavailability of a drug, a pharmacokinetic study must be done to obtain a plasma drug concentration versus time plot for the drug after both intravenous (IV) and non-intravenous administration. The absolute bioavailability is the dose-corrected area under curve (AUC) non-intravenous divided by AUC intravenous. A formulation is said to be bioequivalent in terms of absolute bioavailability to a reference formulation when there is established a 90% confidence interval for $AUC_{(0-\infty)}$ which is between 80% and 125%, relative to degree of bioavailability for the reference formulation.

When pharmacokinetic parameters are given herein (i.e. T_{max}, absolute bioavailability, etc.), it will be understood that they can refer to the mean, median, or individual observed pharmacokinetics, and that mean pharmacokinetics are intended when claimed unless stated to the contrary. The pharmacokinetic parameter will also be understood to be observed in the fasted state, unless otherwise stated.

Discussion

As mentioned above, the invention provides solid oral dosage forms that have improved stability and resistance to oxidative degradation, based on several formulation techniques, including the use of a coating or shell that is substantially impermeable to oxygen, or the use of a lipophilic liquid filling having water homogenized or miscibilized therein. In a first principal embodiment the invention provides a solid oral dosage form comprising: (a) an outer shell or coating having a oxygen permeability of less than about 1.0×10^{-3} ml·cm/(cm^2·24 hr. atm); and (b) an inner fill composition comprising: from about 0.05 to about 2.0 mg. of palonosetron as palonosetron hydrochloride, wherein said palonosetron comprises Cpd1 in an amount of less than 1.0 wt.%; wherein said dosage form exhibits shelf stability, preferably defined so that no more than 5.0 wt.% of said palonosetron hydrochloride degrades when said dosage form is stored three months or greater at 40 °C and 75% RH. 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.

The invention can be practiced with any type of solid oral dosage form, defined as any dosage form that is administered via the oral route and swallowed including, for example, a capsule or gel-cap (i.e. a liquid filled capsule). In a preferred embodiment the dosage form is

a capsule, and in an even more preferred embodiment the dosage form is a liquid filled gel-cap.

Whatever the dosage form, it preferably has an outer shell or coating that has minimal oxygen permeability. In preferred embodiments of the invention, the coating or shell has an oxygen permeability that is less than 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).

A preferred dosage form for the present invention is a capsule having an outer shell that dissolves in gastric fluids. A liquid-filled capsule, preferably including water, is especially preferred because of the uniformity of content and dose when working with liquids, and the ability to minimize oxygen exposure while manufacturing the dosage form and storing the dosage form for prolonged periods of time.

Of the available outer shells, a soft outer shell is a preferred shell structure because of its ability to hold liquids and resist oxygen transmission. Preferred materials for the outer "gel-cap" shell include, for example, gelatin, cellulose, starch, or HPMC. In a preferred embodiment, the shell comprises gelatin, and optionally one or more shell excipients selected from glycerin, sorbitol and titanium dioxide.

The liquid composition that fills the capsule is preferably (1) predominantly lipophilic, and (2) present as a continuous liquid phase (i.e. wherein the liquid components are either miscible or completely homogenized/emulsified). A continuous phase is preferred for ease of processing and composition uniformity. The liquid fill includes the excipient base and the active agent evenly distributed throughout the liquid fill. Furthermore, the active agent is preferably dissolved or dispersed as a microemulsion in the excipient base. The total weight of the fill composition may range is preferably greater than about 50, 75, or 100 mg, and is preferably less than about 500, 250, 200, or 150 mg, most preferably from about 100 to about 150 mg.

The liquid fill is preferably composed predominantly of one or more lipophilic components in an amount of from about 50 wt.% to about 99 wt.%, preferably from about 75 wt.% to about 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 about 1 to about 15 wt.%, more preferably from about 2 to about 10 wt.%. In one preferred embodiment, both the shell and the inner fill composition comprise glycerin. In another preferred embodiment, the liquid fill comprises 0.25, 0.35 mg. or more of palonosetron as

palonosetron hydrochloride (i.e. 0.50 or 0.75 mg.); solubilized in a solubilizing effective amount of a liquid comprising a lipophilic excipient and water.

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 about 0.1 wt.% to about 6 wt.%, from about 0.5 wt.% to about 5 wt.%, or from about 1.0 wt.% to about 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 about 0.05 wt.% to about 30 wt.% water, from about 1 wt.% to about 20 wt.% water, or from about 2 wt.% to about 10 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.

Still further, the excipient base may contain one or more chemical agents to prevent oxygen mediated degradation of the palonosetron in the dosage form. For example, the excipient base may contain a chelating agent such as ethylenediamine tetraacetic acid (EDTA), an antioxidant such as butylated hydroxyanisole (BHA), or a reducing agent, in an amount ranging from about 0.005 wt% to about 2.0 wt.%, more preferably from about 0.01 wt.% to about 1.0 wt.% or from about 0.05 wt.% to about 0.5 wt.%. In a preferred embodiment the excipient base contains an antioxidant.

The active agent, which is preferably palonosetron hydrochloride, is preferably present in the fill composition in an amount ranging from about 0.01 to about 10.0 wt.%, from about 0.05 to about 5.0 wt.%, or from about 0.1 wt% to about 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 about 1 wt.%.

A particularly important feature of the inner fill composition, which is preferred in any of the embodiments of this invention, regardless of dosage form or fill type or method of manufacture, is the minimal content of oxygen. In a preferred embodiment, the inner fill composition comprises oxygen in an amount that degrades no more than about 3.0 wt.%, 2.5 wt.%, 2.0 wt.%, 1.5 wt.%, 1.0 wt.%, or 0.5 wt.%, of said palonosetron, when the dosage form

is stored under shelf stability testing regimens, for example for three months at 40 °C and 75% RH. This amount is preferably measured by the amount of Cpd1 in the composition.

Another important feature of the formulations of the present invention is their pharmacokinetics. It has been determined that the dosage forms of the current invention have an absolute bioavailability of approximately 100%, within the limits of bioequivalence. Thus, for example, whereas a 0.75 mg injection of palonosetron yields a mean $AUC_{(0-\infty)}$ of ca. 58285 (ng· hr/L), a 0.75 mg gel cap yields a mean $AUC_{(0-\infty)}$ of ca. 57403 (ng· hr/L). In contrast, the mean C_{max} for a 0.75 mg gel cap is about 1224 ng/L, whereas a 0.75 mg. injection yields a mean C_{max} of about 1665 ng/L. A 0.50 mg gel cap has been shown to yield a mean $AUC_{(0-\infty)}$ of ca. 38176 (ng· hr/L), and a mean C_{max} of about 810 ng/L, thereby demonstrating dose proportionate pharmacokinetics.

In various embodiments, therefore, the dosage form of the present invention yields greater than 90, 95, or even 98 % absolute bioavailability as an arithmetic mean, again within the limits of bioequivalence. Alternatively or in addition, a 50 mg gel cap yields a mean C_{max} of from about 700 to about 950 ng/ml, or from about 750 to about 875 ng/ml. In a most preferred embodiment, a 50 mg gel gap yields a C_{max} of from 800 to 820 ng/L, preferably within the limits of bioequivalence. Because the dosage forms of the present invention demonstrate dose proportionate pharmacokinetics, it will be understood that these C_{max} values can be standardized based on the strength of the dosage form, and that C_{max} values can be assigned to alternative strengths based upon such standardization.

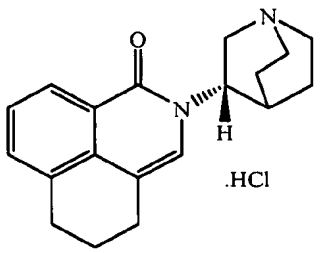
Yet another important feature of the dosage forms of the present invention, which also is preferred in any of the embodiments of the present invention, pertains to the dissolution of the dosage form, and in a preferred embodiment no less than about 75% of the palonosetron in the dosage form dissolves in 30 or 45 minutes when tested in a type II paddle dissolution apparatus according to the U.S. Pharmacopeia, at 75 rpm and 37 °C, in 500 ml. of 0.01N HCl.

Still another feature of the dosage forms of the present invention, which is also preferred in any of the embodiments of the present invention, regardless of dosage form or fill type or method of manufacture, is that the dosage form experiences no more than 5 wt.%, 3 wt.%, or 2 wt.% degradation of the palonosetron when the dosage form in its moisture resistant packaging is exposed to an environment of 25 °C and 60% RH, or 40 °C and 75% RH, for periods equal to or exceeding 3 months, six months, 9 months or even one year.

Palonosetron Hydrochloride and Related Compounds

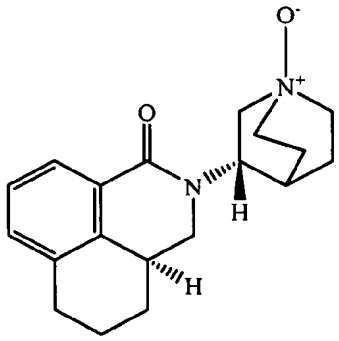
The palonosetron used in the present invention can be palonosetron as a base or pharmaceutically acceptable salt, but is preferably palonosetron hydrochloride. In addition, the palonosetron is preferably present in an amount ranging from about 0.02 mg. to about 10 mg. per dosage form, more preferably from about 0.05 or 0.15 to about 2 mg. per dosage form, and still more preferably from about 0.2 to about 1.0 mg. per dosage form, based on the weight of the base when present as a pharmaceutically acceptable salt. Particularly preferred doses are 0.25 mg, 0.50, and 0.75 mg. of palonosetron or salt thereof, based on the weight of the base. Particularly stable formulations have been found by using palonosetron amounts in liquid gel-caps of greater than about 0.25, 0.35 or 0.45 mg., preferably less than about 2.0 mg.

The palonosetron hydrochloride used to make the dosage form, or contained in the final dosage form, may also be characterized by the presence of various palonosetron related compounds, including compounds Cpd3, Cpd2, and/or Cpd1, as described by the following chemical structures:



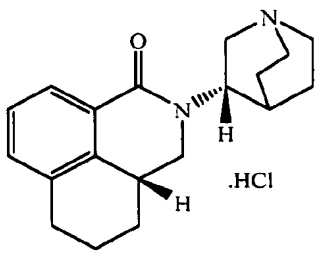
2- [(3S)-1-Azabicyclo [2.2.2]oct-3-yl]-2,4,5,6-tetrahydro-1*H*-benzo[*de*] isoquinoline -1-one hydrochloride

Cpd2



(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

Cpd1



(3aR)-2-[(S)-1-Azabicyclo [2.2.2]oct-3-yl]-2,3,3a,4,5,6-hexahydro-1-oxo-1*H*benz[*de*] isoquinoline hydrochloride

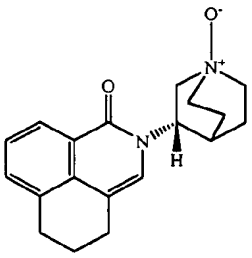
Cpd3

Compounds Cpd2 and Cpd3 are typically present, on an individual or combined basis relative to the palonosetron hydrochloride, in amounts of less that 1.0 wt.%, 0.75 wt.% or 0.5 wt.%, and/or greater than about 0.05 wt.%, 0.075 wt.% or 0.1 wt.%. Cpd2 and Cpd3 can be measured in the dosage form or in the palonosetron raw material used to make the dosage form. Compound Cpd1 is typically present, on an individual basis relative to the palonosetron hydrochloride, in an amount greater than about 0.05 wt.%, 0.1 wt.% or 0.2 wt.%, and/or less than about 3.0 wt.%, 2.5 wt.%, 2.0 wt.%, 1.5 wt.%, 1.0 wt.%, or 0.5 wt.%. Cpd1 is preferably

measured in the dosage form since it is a measure of oxygen mediated degradation. In one preferred embodiment, the dosage forms are defined by a stability in which no more than about 5.0 wt.%, 4.0 wt.%, 3.0 wt.%, 2.5 wt.%, 2.0 wt.%, 1.5 wt.%, 1.0 wt.%, or 0.5 wt.% of compound Cpd1, are formed when the dosage form in its moisture resistant packaging is exposed to an environment of 25 °C and 60% RH, or 40 °C and 75% RH, for periods equal to or exceeding 3 months, 6 months, 9 months or even one year.

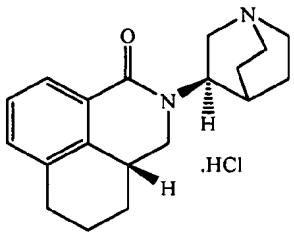
Therefore, in another embodiment the invention provides a solid oral dosage form comprising: (a) from about 0.05 to about 2.0 mg. of palonosetron or a pharmaceutically acceptable salt thereof; (b) one or more pharmaceutically acceptable excipients; (c) Cpd1 in an amount less than 3.0 wt.% based on the weight of the palonosetron. In another embodiment the invention provides a solid oral dosage form comprising: (a) from about 0.05 to about 2.0 mg. of palonosetron or a pharmaceutically acceptable salt thereof; (b) one or more pharmaceutically acceptable excipients; (c) Cpd2 or Cpd3, in an amount less than 1.0 wt.%, based on the weight of the palonosetron or pharmaceutically acceptable salt thereof. In either of these embodiments, the dosage form may optionally comprise means for preventing oxygen mediated degradation of said palonosetron.

Other palonosetron related compounds that can be present in the compositions include Cpd4, Cpd5, Cpd6 and Cpd7, as depicted below:



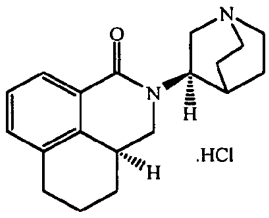
(3S)-3-(1-oxo-2,4,5,6-tetrahydro-1*H*-benzo[*de*] isoquinoline-2-yl)-1-azoniabicyclo[2.2.2]octan-1-olate

Cpd4



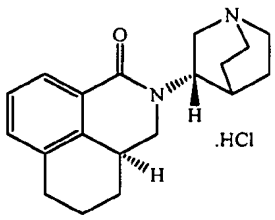
(3aR)-2-[(R)-1-Azabicyclo[2.2.2]oct-3yl]-2,3,3a,4,5,6-hexahydro-1-oxo-1*H*-benz[*de*] isoquinoline hydrochloride

Cpd5



(3aS)-2-[(R)-1-Azabicyclo[2.2.2]oct-3yl]-2,3,3a,4,5,6-hexahydro-1-oxo-1*H*-benz[*de*] isoquinoline hydrochloride

Cpd6



(3aS)-2-[(S)-1-Azabicyclo[2.2.2]oct-3yl]-2,3,3a,4,5,6-hexahydro-1-oxo-1*H*-benz[*de*] isoquinoline hydrochloride

Cpd7

Methods of Making

The invention also provides methods of making palonosetron dosage forms. Thus, in still another embodiment the invention provides a method for manufacturing a batch of palonosetron dosage forms having reduced quantities of impurities and oxygen mediated degradation products comprising (a) mixing palonosetron hydrochloride and one or more pharmaceutically acceptable excipients to form a mixture; (b) processing said mixture into a plurality of final dosage forms; and (c) testing one or more of said final dosage forms for one or more palonosetron related compounds selected from Cpd2, Cpd1, and Cpd3. "Processing" refers to the steps used to prepare a pharmaceutical formulation and final dosage form from a defined set of ingredients, and excludes the processes of chemically synthesizing the ingredients used in the formulation. This embodiment extends to all dosage forms of palonosetron, including single unit dose ampoules of palonosetron filled, for example, with a sterile injectable liquid. Thus, for example, the invention may be extended to methods for filling unit dose ampoules or containers with sterile injectable solutions of palonosetron, preferably in aqueous media, and preferably formulated as described in WO 2004/067005 of Calderari et al. In this context, an "ampoule" means a small sealed container of medication that is used one time only, and includes breakable and non-breakable glass ampoules, breakable plastic ampoules, miniature screw-top jars, and any other type of container of a size capable of holding only one unit dose of palonosetron (typically about 5 mls.).

Another embodiment captures the balance achieved by the formulations of the present invention, relative to bioavailability and stability, and in this embodiment the invention provides a method of optimizing the bioavailability and stability of palonosetron in a palonosetron gelatin capsule comprising: (a) providing a soft gelatin outer shell having an oxygen permeability of less than about 1.0×10^{-3} ml·cm/(cm^2·24 hr. atm); and (b) preparing a fill composition by steps comprising: (i) providing from about 0.05 to about 2.0 mg. of palonosetron as palonosetron hydrochloride, wherein said palonosetron comprises Cpd1 in an amount of less than 1.0 wt.% based on the weight of said palonosetron; (ii) dissolving or dispersing said palonosetron in water to form an aqueous premix; (iii) mixing said aqueous premix with one or more lipophilic excipients, at a weight ratio of aqueous premix to lipophilic excipients of less than 50:50. 40:60, 30:70, or 20:80, to form a miscible or homogenous lipophilic fill composition; (iv) mixing a surfactant with said water, said aqueous premix, or said fill composition; and (v) balancing the quantities of surfactant and water in said fill composition to facilitate the bioavailability of palonosetron from said gelatin capsule when orally ingested, and to minimize the degree of palonosetron degradation; and (c) filling said outer shell with said fill composition.

Still another method of the present invention comprises a method of packaging a palonosetron dosage form comprising: (a) providing an empty shell; and (b) filling said shell container with a fill composition in an oxygen depleted ambient environment, wherein said fill composition comprises: (i) a defined amount of an active ingredient composition comprising palonosetron or a pharmaceutically acceptable salt thereof; and (ii) a pharmaceutically acceptable excipient. An "oxygen depleted environment" is preferably one defined by an oxygen content of less than about 10% oxygen, 5% oxygen, or even 1% or 0.1% oxygen (on a weight or volume basis). In an even more preferred embodiment, the methods of making or packaging the dosage forms of the present invention are performed under a nitrogen blanket or purge, in a nitrogen rich environment comprising greater than about 90%, 95%, or 98% nitrogen (on a weight or volume basis).

In another particular embodiment, the method is defined by the variability of active ingredient among dosage forms, in which there is provided a method of making a plurality of solid oral dosage forms comprising: (a) providing a capsule shell; (b) filling said shell with a fill composition comprising: (i) a defined amount of palonosetron or a pharmaceutically acceptable salt thereof; and (ii) a pharmaceutically acceptable excipient; and (c) repeating steps (a) and (b) one or more additional times, wherein said defined amount has a capsule to capsule variability of less than about 3, 2, 1, 0.5 or 0.1 wt.%.

In any of the foregoing embodiments, the method of making may also further comprise packaging said dosage form or plurality of dosage forms in a moisture resistant sealed container. The material used to form the moisture resistant sealed container preferably has an oxygen permeability less than about 1.0×10^{-2}, 1.0×10^{-3}, 1.0×10^{-4}, or even 5.0×10^{-5} ml·cm/(cm^2·24 hr. atm). Alternatively or in addition, the packaging can be characterized as a "tight container" under standards described in USP <671> (i.e. not more than one of ten test containers exceeds 100 mg. per day per L in moisture permeability, and none exceeds 200 mg. per day per ml.). Still further, the container can be defined by the amount of moisture that it allows the dosage forms of the invention to absorb during storage. For example, in various preferred embodiments, the container prevents said doses from absorbing more than 1.0, 0.1 or even 0.05 wt.% moisture in three months when stored at 40 °C and 75% relative humidity. Blister packaging is a particularly preferred mode of packaging.

Soft Gelatin Capsules

The liquid core pharmaceutical compositions of the present invention are encapsulated in a soft gelatin shell described below. Gelatin is a preferred component of the soft gelatin shells of the instant invention. The starting gelatin material may be obtained by the partial hydrolysis of collagenous material, such as the skin, white connective tissues, or bones of animals. Gelatin material can be classified as Type A gelatin, which is obtained from the acid-processing of porcine skins and exhibits an isoelectric point between pH 7 and pH 9; and Type B gelatin, which is obtained from the alkaline-processing of bone and animal (bovine) skins and exhibits an isoelectric point between pH 4.7 and pH 5.2. Blends of Type A and Type B gelatins can be used to obtain a gelatin with the requisite viscosity and bloom strength characteristics for capsule manufacture. Gelatin suitable for capsule manufacture is commercially available from the Sigma Chemical Company, St. Louis, Mo. For a general description of gelatin and gelatin-based capsules, see Remington's Pharmaceutical Sciences, 16th ed., Mack Publishing Company, Easton, Pa. (1980), page 1245 and pages 1576-1582; and U.S. Pat. No. 4,935,243, to Borkan et at., issued Jun. 19, 1990; these two references being incorporated herein by reference in their entirety.

The soft gelatin shells may comprise from about 20% to about 60% gelatin. The gelatin can be of Type A or Type B, or a mixture thereof with bloom numbers ranging from about 60 to about 300. The soft gelatin shells may also comprise a plasticizer. Useful plasticizers include glycerin, sorbitan, sorbitol, or similar low molecular weight polyols, and mixtures thereof. A preferred plasticizer useful in the present invention is glycerin. The soft gelatin shells of the

instant invention may also comprise water. Without being limited by theory, the water is believed to aid in the rapid dissolution or rupture of the soft gelatin shell upon contact with the gastrointestinal fluids encountered in the body.

Soft gelatin capsules and encapsulation methods are described in P. K. Wilkinson et at., "Softgels: Manufacturing Considerations", Drugs and the Pharmaceutical Sciences, 41 (Specialized Drug Delivery Systems), P. Tyle, Ed. (Marcel Dekker, Inc., New York, 1990) pp.409-449; F. S. Horn et at., "Capsules, Soft", Encyclopedia of Pharmaceutical Technology, vol. 2, J. Swarbrick and J. C. Boylan, eds. (Marcel Dekker, Inc., New York, 1990) pp. 269-284; M. S. Patel et at., "Advances in Softgel Formulation Technology", Manufacturing Chemist, vol. 60, no. 7, pp. 26-28 (July 1989); M. S. Patel et al., "Softgel Technology", Manufacturing Chemist, vol. 60, no. 8, pp. 47-49 (August 1989); R. F. Jimerson, "Softgel (Soft Gelatin Capsule) Update", Drug Development and Industrial Pharmacy (Interphex '86 Conference), vol. 12, no. 8 & 9, pp. 1133-1144 (1986); and W. R. Ebert, "Soft Elastic Gelatin Capsules: A Unique Dosage Form", Pharmaceutical Technology, vol. 1, no. 5, pp. 44-50 (1977); these references are incorporated by reference herein in their entirety. The resulting soft gelatin capsule is soluble in water and in gatrointestinal fluids. Upon swallowing the capsule, the gelatin shell rapidly dissolves or ruptures in the gastrointestinal tract thereby introducing the pharmaceutical actives from the liquid core into the body.

Methods of Treatment

In still further embodiments, the invention provides methods of treating emesis by administering one or more of the dosage forms described herein. 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").

Bioequivalence Testing

When a product is said to exhibit a particular pharmacokinetic parameter "within the limits of bioequivalence," it will be understood that the product is bioequivalent to a test drug employing the bioequivalence testing specified herein. Bioequivalence testing typically requires an in vivo test in humans in which the concentration of the active ingredient or active moiety, and, when appropriate, its active metabolite(s), in whole blood, plasma, serum, or

other appropriate biological fluid is measured as a function of time. Defined as relative bioavailability ("BA"), bioequivalence ("BE") involves a comparison between a test and reference drug product. Although BA and BE are closely related, BE comparisons normally rely on (1) a criterion, (2) a confidence interval for the criterion, and (3) a predetermined BE limit.

A standard in vivo BE study design is based on the administration of either single or multiple doses of the test and reference products to healthy subjects on separate occasions, with random assignment to the two possible sequences of drug product administration. Statistical analysis for pharmacokinetic measures, such as area under the curve (AUC) and peak concentration (C_{max}), is preferably based on the so-called "two one-sided tests procedure" to determine whether the average values for the pharmacokinetic measures determined after administration of the test and reference products are comparable. This approach is termed average bioequivalence and involves the calculation of a 90% confidence interval for the ratio of the averages (population geometric means) of the measures for the test and reference products. To establish BE, the calculated confidence interval should fall within a BE limit, i.e. 80-125% for the ratio of the product averages. Thus, for example, bioequivalence is said to be established under a given set of circumstances by a 90% confidence interval for AUC which is between 80% and 125%, and a 90% confidence interval for C_{max} which is between 80% and 125%.

Further detail regarding BE procedures can be found in FDA's July 1992 Guidance Document entitled "Statistical Procedures for Bioequivalence Studies Using a Standard Two-Treatment Crossover Design," the contents of which are incorporated herein by reference.

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 – Representative Gel-cap Formulation

Table 1 describes representative formulations for a gel-cap solid oral dosage form containing 0.25, 0.50 and 0.75 mg. of palonosetron.

Table 1. Representative Gel-cap Formulation

Names of Ingredients	Formula (mg per capsule)		
	0.25 mg	0.50 mg	0.75 mg
Active drug substance Palonosetron HCl	0.28[a]	0.56[b]	0.84[c]
Excipients Purified water	5.57	5.57	5.57
Glycerin, anhydrous	6.40	6.40	6.40
Butylated hydroxyanisole (BHA)	0.13	0.13	0.13
Polyglyceryl oleate (Plurol Oleique CC 497)	6.65* (1.66)**	6.65* (1.66)**	6.65* (1.66)**
Mono- and di-glycerides of Capryl/Capric Acid (Capmul MCM)	113.97* (118.96)**	113.69* (118.68)**	113.41* (118.40)**
Nitrogen	---	---	---
Theoretical fill weight	133.00 mg	133.00 mg	133.00 mg
Gelatin Capsule Shell, #3, oval (Cardinal Health)	1 capsule	1 capsule	1 capsule

[a] corresponding to 0.25 mg free base
[b] corresponding to 0.50 mg free base
[c] corresponding to 0.75 mg free base
* Formulation A (clinical batch)
** Formulation B (commercial batch)

Example 2 – Manufacturing Protocol

The compounding process involves the formulation of two separate mixes, the side mix containing the active ingredient, glycerin and water, and the main mix containing the remaining excipients. The process starts with the two separate mixes which are later combined to comprise the final fill solution for encapsulation. The fill solution is blanketed with nitrogen during the compounding and encapsulation phases.

Example 3 – Representative Dissolution Test Protocol

An exemplary dissolution method for Palonosetron Oral Capsules, 0.25 mg, 0.50 mg, and 0.75 mg uses USP Apparatus 2 (paddles) at 75 rpm in 500 mL of 0.01N HCl with a dissolution temperature of 37.0 ± 0.5°C. The acceptance criterion is "Not less than 75 % at 45 minutes".

Six softgel-capsules are individually weighed. Softgel-capsules are placed in each vessel, and sampled at 15, 30, 45, and 60 minutes. Sampling at 15, 30, 60 minutes is for

information only. Sample solutions are withdrawn and filtered through online filters into test tubes or HPLC vials. The samples are analyzed using a HPLC system with UV detector.

Table 2. Dissolution Conditions

USP Apparatus	2 Paddles
Medium	0.01N HCl, 500 mL
Temperature	37 ± 0.5°C
Rotation Speed	75 rpm
Sampling Times	45 minutes 15, 30, and 60 minutes (for information only)
Sampling Volume	3 mL (or 1 – 1.5 mL when collected directly into HPLC vials)
Volume	500 mL dissolution medium

Example 4 -- Chemical and Physical Stability

Table 3 presents the results of chemical and physical stability testing for the 0.75 mg. palonosetron softgel formulations reported in Example 1, packaged in a 2x5 Blister Unit (Forming: LM 15088, Foil: Reynolds 701).

Table 3. Chemical and Physical Stability

Test	Palonosetron assay		Palonosetron related substances			Dissolution test (% dissolved)			
						45 min.	15 min.	30 min.	60 min.
Provisional Specification	90.0-110.0 %	% vs t0	Cpd3	Cpd2	Cpd1	NLT 75%	For inform. Only	For inform. only	For inform. only
			≤ 0.50%	≤ 0.50%	≤ 3.0%				
Initial values	97.7	100.0	0.28	0.28	0.20	98.5	70.4	97.7	98.9
25°C/60% r.h.									
03 months	97.6	99.9	0.23	0.26	0.23	99.2	97.6	99.1	98.8
06 months	96.5	98.8	0.26	0.27	0.46	97.6	87.4	97.2	97.7
09 months	96.0	98.3	0.23	0.27	0.6	99.0	80.5	98.9	99.1
12 months	93.7	95.9	0.22	0.26	0.6	96.8	81.9	96.5	96.7
40°C/75% r.h.									
01 month	97.2	99.5	0.36	0.25	0.56	99.9	92.3	100.5	100.1
03 months	97.5	99.8	0.24	0.26	0.65	97.3	79.9	97.0	97.5
06 months	96.2	98.5	0.26	0.27	0.68	96.9	52.5	96.7	97.0

Example 5 -- Chemical and Physical Stability

Table 4 presents the results of chemical and physical stability testing for the 0.50 mg. palonosetron softgel formulations reported in Example 1, packaged in a 2x5 Blister Unit (Forming: LM 15088, Foil: Reynolds 701).

Table 4. Chemical and Physical Stability

Test	Palonosetron assay		Palonosetron related substances			Dissolution test (% dissolved)			
Provisional Specification	90.0-110.0 %	% vs t0	Cpd3	Cpd2	Cpd1	45 min.	15 min.	30 min.	60 min.
			≤ 0.50%	≤ 0.50%	≤ 3.0%	NLT 75%	For inform. only	For inform. only	For inform. only
Initial values	97.9	100.0	0.28	0.26	0.16	98.9	69.1	99.9	99.2
25°C/60% r.h.									
03 months	97.5	99.6	0.23	0.26	0.44	100.1	86.0	100.0	100.1
06 months	97.2	99.3	0.27	0.28	0.37	97.6	41.4	88.3	97.6
09 months	96.5	98.6	0.22	0.28	0.5	99.0	83.0	97.8	99.1
12 months	94.7	96.7	0.22	0.27	0.5	96.9	85.6	96.7	97.0
40°C/75% r.h.									
01 month	97.3	99.4	0.29	0.27	0.42	102.6	65.8	101.1	102.8
03 months	97.3	99.4	0.24	0.26	0.55	100.0	39.8	94.2	99.0
06 months	96.6	98.7	0.26	0.27	0.67	97.0	52.7	96.7	97.2

Example 6 -- Chemical and Physical Stability

Table 5 presents the results of chemical and physical stability testing for the 0.25 mg. palonosetron softgel formulations reported in Example 1, packaged in a 2x5 Blister Unit (Forming: LM 15088, Foil: Reynolds 701).

Table 5. Chemical and Physical Stability

Test	Palonosetron assay		Palonosetron related substances			Dissolution test (% dissolved)			
						45 min.	15 min.	30 min.	60 min.
Provisional Specification	90.0-110.0 %	% vs t0	Cpd3	Cpd2	Cpd1	NLT 75%	For inform. only	For inform. only	For inform. only
			≤ 0.50%	≤ 0.50%	≤ 3.0%				
Initial values	97.7	100.0	0.29	0.29	0.38	97.2	61.8	97.4	97.7
25°C/60% r.h.									
03 months	97.4	99.7	0.24	0.26	0.92	98.6	98.0	99.1	99.1
06 months	95.9	98.2	0.28	0.27	1.10	95.2	82.3	94.8	95.7
09 months	94.7	96.9	0.21	0.28	1.4	94.5	89.2	93.9	94.6
12 months	94.5	96.7	0.23	0.27	1.7	96.2	97.1	96.1	96.1
40°C/75% r.h.									
01 month	96.3	98.6	0.29	0.27	1.42	99.4	88.2	99.5	97.7
3 months	97.4	99.7	0.24	0.25	1.85	97.4	78.7	97.6	97.5
6 months	94.0	96.2	0.27	0.26	1.94	96.8	82.6	96.2	97.0

Example 7 -- Representative Injectable Formulation

The following Table 6 describes a representative injectable formulation containing palonosetron.

Table 6. Representative Injectable Formulation

Ingredient	mg/mL
Palonosetron Hydrochloride	0.05 (calculated as base)
Mannitol	41.5
EDTA	0.5
Trisodium citrate	3.7
Citric acid	1.56
WFJ	1.0
Sodium hydroxide solution and/or hydrochloric acid solution	pH 5.0 ± 0.5
Flavoring	q.s.

Example 8 – Identification and Assay of Palonosetron in Palonosetron HCl Softgels by HPLC with UV Detector

Testing procedure
Prepare Sample and Standard solutions at the Palonosetron HCl nominal concentration of 6.25 µg/mL in HCl 0.01 N.
Filter solution and inject into HPLC system.

HPLC Condition

Column	C8, 250 mm x 4.6 mm (i.d.)
Column Temperature	30°C
Mobile Phase	ACN/H_2O/ TFA, Gradient Elution
Flow rate	1 mL/min
Detection	UV at 210 nm
Injection Volume	20 µL

Example 9 – Determination of Palonosetron Related Compounds in Palonosetron HCl Softgels and the In-Process Assay of the Softgels Fill Solution

Testing procedure
Prepare Sample and Standard solutions at the Palonosetron HCl nominal concentration of 0.15 mg/mL in Methanol.
Inject solutions directly into HPLC system.

HPLC Condition

Column	C8, 250 mm x 4.6 mm (i.d.)
Column Temperature	30°C
Mobile Phase	ACN/H_2O/ TFA, Gradient Elution
Flow rate	1 mL/min
Detection	UV at 210 nm
Injection Volume	10 µL

Example 10 – Determination of Palonosetron Related Compounds in Palonosetron HCl Softgels by Chiral HPLC with UV Detector

Testing procedure
Prepare Sample solution at the Palonosetron HCl nominal concentration of 0.34 mg/mL in Methanol.
Prepare Cpd2 Standard solution at the nominal concentration of 5.6 µg/mL.
Prepare Resolution solution, in methanol solvent, at the nominal concentration of 8 µg/mL:Cpd2, Cpd4, Cpd5, Cpd6 and Cpd7 concentration approx. 0.4 µg/mL.
Inject solutions directly into HPLC system.

HPLC Condition

Column	Chiral column
Column Temperature	35°C
Mobile Phase	ACN/MeOH/ IPA/AcOH/TEA, Isocratic elution
Flow rate	1 mL/min
Detection	UV at 238 nm
Injection Volume	10 µL

Example 11 – Dissolution of Palonosetron HCl Softgels with Assay by HPLC

Testing procedure
Prepare Standard solutions at the Palonosetron HCl nominal concentration of 1 µg/mL in HCl 0.01 N.
Sample solution: place one softgel-capsule into a vessel containing 500 mL of 0.01 N HCl.
Filter solutions and inject into HPLC system.

HPLC Condition

Column	C8, 150 mm x 4.6 mm (i.d.)
Column Temperature	30°C
Mobile Phase	ACN/H_2O/ TFA, Gradient Elution
Flow rate	1 mL/min
Detection	UV at 210 nm
Injection Volume	50 µL

Example 12 – Bioequivalence of 0.75 mg. gel cap and injection dosage forms

Bioequivalence and absolute bioavailability were tested in a single oral dose of two formulations of 0.75 mg palonosetron in healthy volunteers. The study was a three treatment, three period, two sequence cross-over study.

Treatment A represented a single dose of 0.75 mg of palonosetron in the clinical gel-cap formulation described in Table 1.

Treatment B represented a single dose of 0.75 mg of palonosetron in the commercial gel-cap formulation in Table 1.

Treatment IV consisted of three consecutive bolus injections of Aloxi 25 mg.

Pharmacokinetic parameters are reported below in Table 7:

Table 7

Pharmaco-kinetic parameter **Palonosetron [unit]**		**0.75 mg Palonosetron oral administration (formulation A)** **N=33**	**0.75 mg Palonosetron oral administration (formulation B)** **N=33**	**0.75 mg Palonosetron intravenous administration (3 x 0.25 mg i.v. Aloxi®)** **N=30**
$AUC_{(0-t)}$ [ng·h/L]	Mean (SD)	53835 (17961)	55235 (17817)	53088 (15233)
	Geo.Mean (Geo.SD)	50716 (1.44)	52536 (1.39)	50793 (1.37)
	Median	50978	53325	50984
	Minimum-Maximum	16971 - 96273	20951 - 111916	20609 - 78424
$AUC_{(0-\infty)}$ [ng·h/L]	Mean (SD)	57403 (17898)	58285 (18110)	56480 (15343)
	Geo.Mean (Geo.SD)	54539 (1.40)	55638 (1.37)	54324 (1.34)
	Median	54614	56802	54011
	Minimum-Maximum	18773 - 100234	24473 - 114765	24142 - 81547
C_{max} [ng/L]	Mean (SD)	1223.985 (348.324)	1200.620 (324.606)	1665.314 (527.638)
	Geo.Mean (Geo.SD)	1178.670 (1.32)	1160.078 (1.31)	1588.758 (1.37)
	Median	1208.136	1133.115	1628.480
	Minimum-Maximum	570.494-2365.980	571.922-2130.740	890.742-2789.077
t_{max} [h]	Median	4.520	4.530	0.250
	Minimum-Maximum	2.000 - 8.000	2.000 - 12.030	0.250 - 4.030

Pharmacokinetics are also reported in figure 1, wherein b1 represents treatment by Formulation A, b2 represents treatment by Formulation B, and b3 represented treatment by

Aloxi i.v. The figure reports arithmetic mean plasma concentrations of palonosetron (ng/ml) versus time (H) on a linar scale (n=33).

Example 13 – Boequivalence of 50 mg. clinical and commercial gel cap formulations

A bioequivalence study was undertaken to evaluate single oral doses of two formulations (Formulation A and Formulation B) of palonosetron 0.50 mg. Soft gel capsules in healthy male and female subjects. The study was a two treatments, two periods, two sequences, open label, randomized cross-over study.

Pharmacokinetic results are reported in Table 8.

Table 8

Pharmaco-kinetic parameter Palonosetron [unit]		**0.50 mg Palonosetron oral administration (formulation A) N=36**	**0.50 mg Palonosetron oral administration (formulation B) N=36**
AUC_{0-t} [ng·h/L]	Mean (SD)	34076 (9874)	35106 (11012)
	Geo. Mean (Geo. SD)	32766 (1.33)	33530 (1.36)
	Median	33641	34981
	Minimum-Maximum	20085 - 60189	19003 - 72136
$AUC_{0-\infty}$ [ng·h/L]	Mean (SD)	37099 (10141)	38176 (11698)
	Geo. Mean (Geo. SD)	35834 (1.30)	36555 (1.35)
	Median	36859	37627
	Minimum-Maximum	22439 - 62727	21240 - 77635
C_{max} [ng/L]	Mean (SD)	785.241 (182.437)	810.176 (165.985)
	Geo. Mean (Geo. SD)	765.702 (1.25)	793.900 (1.23)
	Median	750.344	816.457
	Minimum-Maximum	463.862 - 1322.774	537.047 - 1258.878
t_{max} [h]	Median	5.500	5.000
	Minimum-Maximum	2.000 - 8.000	2.000 - 8.000

Pharmacokinetic parameters are also reported in figure 2, wherein b1 represents clinical formulation A. and b2 represents commercial formulation B. The figure reports arithmetic mean plasma concentrations of palonosetron (ng/ml) versus time (H) on a linar scale (n=33).

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

What is claimed is:

1) A soft gelatin capsule for oral administration comprising:
   a) a soft gelatin outer shell having an oxygen permeability of less than about 1.0×10^{-3} ml·cm/(cm^2·24 hr. atm); and
   b) a lipophilic liquid inner fill composition comprising:
      i) greater than about 50 wt.% of one or more lipophilic components;
      ii) from about 1 to about 20 wt.% of water miscibilized or homogenized in said one or more lipophilic components;
      iii) from about 0.05 to about 2.0 mg. of palonosetron as palonosetron hydrochloride solubilized or dispersed in said water; and
      iv) a surfactant.

   wherein said capsule exhibits pharmacokinetics when orally ingested in a fasted state that are bioequivalent to a formulation having greater than 95% absolute bioavailability, wherein bioequivalence is established by a 90% confidence interval for AUC which is between 80% and 125%.

2) The capsule of claim 1 wherein said inner fill composition comprises:
   a) from 0.5 to 1.0 mg. of palonosetron as palonosetron hydrochloride; and
   b) a solubilizing effective amount of a liquid comprising a lipophilic excipient and water.

3) The soft gelatin capsule of claim 1 comprising glycerin in said outer shell and said inner fill composition.

4) The soft gelatin capsule of claim 1, wherein:
   a) said inner fill composition further comprises an antioxidant or a reducing agent;
   b) said palonosetron comprises less than about 1 wt.% of Cpd1.

5) The capsule of claim 1 exhibiting pharmacokinetics when orally ingested in a fasted state that are bioequivalent to a formulation having greater than 95% absolute bioavailability, and a C_{max} of from 800 to 820 ng/L, wherein bioequivalence is established by:

a) a 90% confidence interval for AUC which is between 80% and 125%, and

b) a 90% confidence interval for C_{max} which is between 80% and 125%.

6) The capsule of claim 1 wherein said inner fill composition comprises oxygen in an amount that mediates no more than about 3.0 wt.% oxidative degradation when said dosage form is stored for three months at 40 °C and 75% RH.

7) The capsule of claim 1 wherein no less than about 75% of said palonosetron or pharmaceutically acceptable salt thereof dissolves in 45 minutes when tested in a type II paddle dissolution apparatus according to the U.S. Pharmacopeia, at 75 rpm and 37 °C, in 500 ml. of 0.01N HCl.

8) The capsule of claim 1 wherein no less than about 75% of said palonosetron or pharmaceutically acceptable salt thereof dissolves in 30 minutes when tested in a type II paddle dissolution apparatus according to the U.S. Pharmacopeia, at 75 rpm and 37 °C, in 500 ml. of 0.01N HCl.

9) The capsule of claim 1 wherein said shell has an oxygen permeability of less than about 1.0×10^{-4} ml·cm/(cm^2·24 hr. atm).

10) The capsule of claim1 wherein said inner fill comprises from 0.5 to 4 wt.% of a surfactant.

11) A liquid filled soft capsule dosage form for oral administration comprising:

a) an outer shell having a oxygen permeability of less than about 1.0×10^{-3} ml·cm/(cm^2·24 hr. atm); and

b) an inner fill composition comprising from about 0.05 to about 2.0 mg. of palonosetron or pharmaceutically acceptable salt thereof, wherein said palonosetron or pharmaceutically acceptable salt thereof comprises Cpd1 of a pharmaceutically acceptable salt thereof in an amount of less than 1.0 wt.% based on the weight of said palonosetron.

wherein said inner fill composition comprises oxygen in an amount that mediates no more than about 3.0 wt.% oxidative degradation of said palonosetron or pharmaceutically acceptable salt thereof when said dosage form is stored three months or greater at 40 °C and 75% RH.

12) The capsule of claim 11 exhibiting pharmacokinetics when orally ingested in a fasted state that are bioequivalent to a formulation having greater than 90%

absolute bioavailability wherein bioequivalence is established by a 90% confidence interval for AUC which is between 80% and 125%.

13) The capsule of claim 11 wherein said inner fill composition comprises from about 1 wt.% to about 20 wt.% water.

14) The capsule of claim 11 exhibiting pharmacokinetics when orally ingested in a fasted state that are bioequivalent to a formulation having greater than 95% absolute bioavailability, and a C_{max} of from 800 to 820 ng/L, wherein bioequivalence is established by:

a) a 90% confidence interval for AUC which is between 80% and 125%, and

b) a 90% confidence interval for C_{max} which is between 80% and 125%.

15) The capsule of claim 11 wherein no less than about 75% of said palonosetron or pharmaceutically acceptable salt thereof dissolves in 45 minutes when tested in a type II paddle dissolution apparatus according to the U.S. Pharmacopeia, at 75 rpm and 37 °C, in 500 ml. of 0.01N HCl.

16) The capsule of claim 11 wherein said shell has an oxygen permeability of less than about 1.0×10^{-4} ml·cm/(cm^2·24 hr. atm).

17) The capsule of claim 11 wherein:

a) said inner fill composition comprises glycerin; an

b) said shell comprises glycerin.

18) The capsule of claim 11 wherein said shell comprises gelatin, cellulose, starch or HPMC.

19) A method of optimizing the bioavailability and stability of palonosetron in a palonosetron gelatin capsule comprising:

a) providing a soft gelatin outer shell having an oxygen permeability of less than about 1.0×10^{-3} ml·cm/(cm^2·24 hr. atm); and

b) preparing a fill composition by steps comprising:

i) providing from about 0.05 to about 2.0 mg. of palonosetron as palonosetron hydrochloride wherein said palonosetron comprises Cpd1 in an amount of less than 3.0 wt.%;

ii) dissolving or dispersing said palonosetron in water to form an aqueous premix;

iii) mixing said aqueous premix with one or more lipophilic excipients, at a weight ratio of aqueous premix to lipophilic excipients of less than 30:70, to form a miscible or homogenous lipophilic fill composition;

iv) mixing a surfactant with said water, said aqueous premix, or said fill composition; and

v) balancing the quantities of surfactant and water in said fill composition to facilitate the bioavailability of palonosetron from said gelatin capsule when orally ingested, and to minimize the degree of palonosetron degradation; and

c) filling said outer shell with said fill composition.

20) The method of claim 19 wherein said fill composition comprises from about 0.1 to about 10.0 wt.% surfactant, and from about 0.1 to about 20 wt.% water.

21) The method of claim 19 wherein said fill composition comprises from about 0.5 to about 4 wt.% surfactant, and from about 1 to about 10 wt.% water.

22) The method of claim 19 wherein said outer shell further comprises glycerin, further comprising mixing said aqueous premix with glycerin, before or after the formation of said lipophilic fill composition.

23) A method of making a batch of palonosetron dosage forms having reduced quantities of impurities and oxygen mediated degradation products comprising:

a) mixing palonosetron hydrochloride and one or more pharmaceutically acceptable excipients to form a mixture;

b) processing said mixture into a plurality of final dosage forms; and

c) testing one or more of said final dosage forms for one or more palonosetron related compounds selected from Cpd1, Cpd2, and Cpd3, or the hydrochloride salt thereof.

24) The method of claim 23 comprising testing for Cpd1 or the hydrochloride salt thereof.

25) The method of claim 23 comprising testing for Cpd2 or the hydrochloride salt thereof.

26) The method of claim 23 comprising testing for Cpd3 or the hydrochloride salt thereof.

27) The method of claim 23, further comprising testing said palonosetron hydrochloride or said final dosage form for one or more compounds selected from Cpd4, Cpd5, Cpd6, or Cpd7, or the hydrochloride salt thereof.

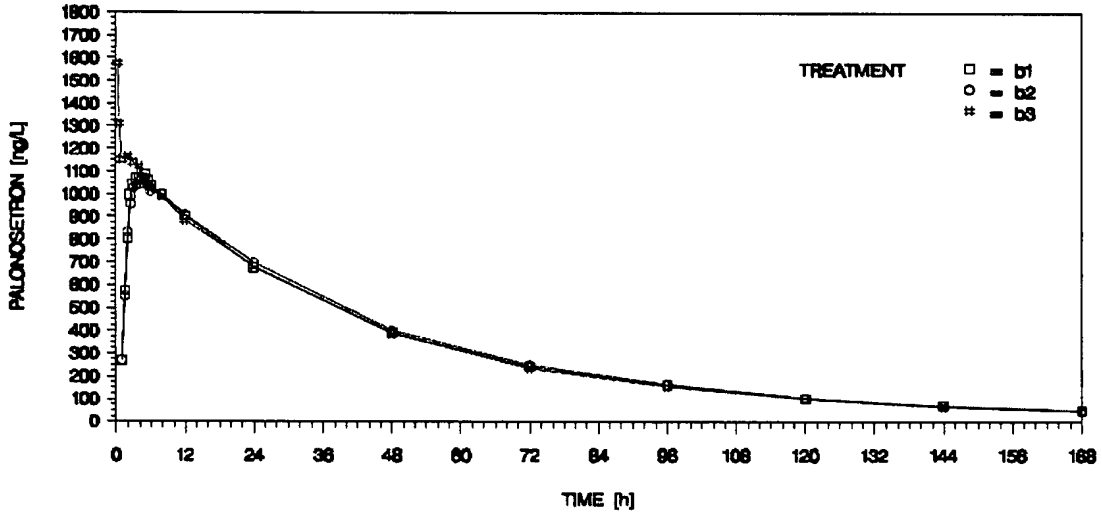


FIGURE 1

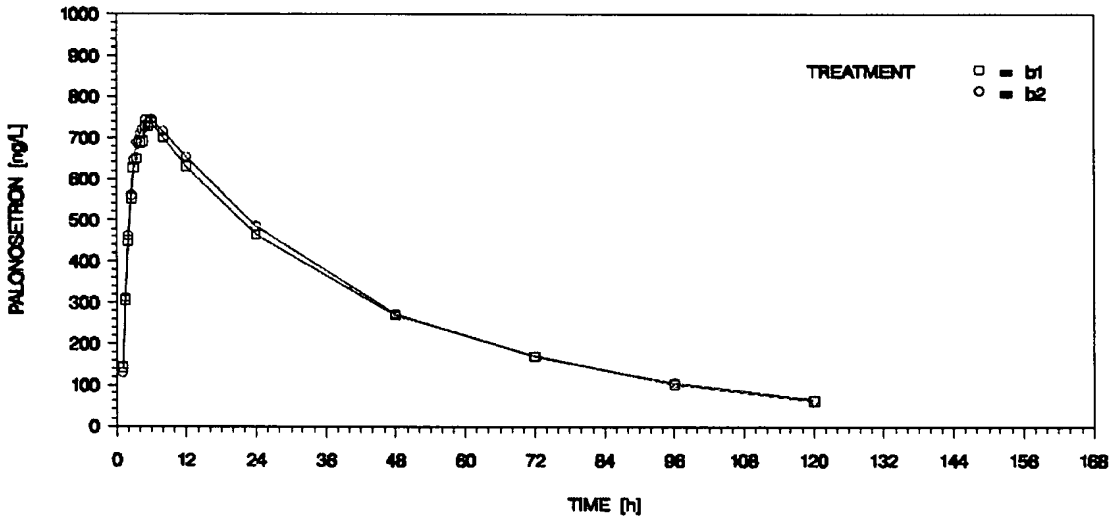


FIGURE 2

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2007/009098

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/48 A61K9/66 A61K31/473

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2004/045615 A (HELSINN HEALTHCARE SA [CH]; MACCIOCCHI ALBERTO [CH]; CANTOREGGI SERGIO) 3 June 2004 (2004-06-03) page 14, line 11 - line 13	1-27
A	WO 2005/065652 A (FRIEDMAN DORON [IL]) 21 July 2005 (2005-07-21) page 9, paragraph 5; examples	1-27
A	WO 02/053131 A (CLL PHARMA [FR]; ABOU CHACRA-VERNET MARIE-LINE [FR]; LARUELLE CLAUDE [) 11 July 2002 (2002-07-11) page 9, line 26 - line 28; examples	1-27

☐ Further documents are listed in the continuation of Box C.

☒ 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

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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"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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 January 2008	28/01/2008

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, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	GIMENEZ MIRALLES, J

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2007/009098

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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(71) Applicant *(for all designated States except US)*: **HELSINN HEALTHCARE SA** [CH/CH]; P. O. Box 357, CH-6915 Pambio-Noranco (CH).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **CALDERARI, Giorgio** [CH/CH]; Via Scer, CH-6862 Rancate (CH). **BONADEO, Daniele** [IT/IT]; Via Ronco Capo Caccia, 32, Casalzuigno, I-21030 Varese (IT). **CANNELLA, Roberta** [IT/IT]; Via Europa, 50, Morazzone, I-21040 Varese (IT). **BRAGLIA, Enrico** [CH/CH]; Via Pian Scairolo 9, CH-6912 Pazzallo (CH). **BRAGLIA, Riccardo** [CH/CH]; Via Pian Scairolo 9, CH-6912 Pazzallo (CH).

(74) Agent: **LEISSLER-GERSTL, Gabriele**; Eisenführ, Speiser & Partner, Arnulfstrasse 25, 80335 München (DE).

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(54) Title: LIQUID PHARMACEUTICAL FORMULATIONS OF PALONOSETRON

(57) Abstract: The present invention relates to shelf-stable liquid formulations of palonosetron for reducing chemotherapy and radiotherapy induced emesis with palonosetron. The formulations are particularly useful in the preparation of intravenous and oral liquid medicaments.

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LIQUID PHARMACEUTICAL FORMULATIONS OF PALONOSETRON

FIELD OF THE INVENTION

The present invention relates to shelf-life stable liquid formulations of palonosetron that are especially useful in the preparation of injectable and oral medicaments.

BACKGROUND OF THE INVENTION

Emesis is a devastating consequence of cytotoxic therapy, radiotherapy, and post-operative environments that drastically affects the quality of life of people undergoing such treatments. In recent years a class of drugs referred to as 5-HT_3 (5-hydroxytryptamine) receptor antagonists has been developed that treat such emesis by antagonizing cerebral functions associated with the 5-HT_3 receptor. See *Drugs Acting on 5-Hydroxytryptamine Receptors*: The Lancet Sep. 23, 1989 and references cited therein. Drugs within this class include ondansetron, granisetron, alosetron, tropisetron, and dolasetron. These 5-HT_3 antagonists are often administered intravenously shortly before chemotherapy or radiotherapy is initiated, and can be administered more than once during a cycle of chemotherapy or radiotherapy. In addition, they are often supplied as tablets or oral elixirs to either supplement an intravenous administration, or to ease home usage of the drug if the patient is self-administering the chemotherapeutic regimen.

Because some chemotherapeutic agents can induce emesis over extended periods of several days even when they are administered only once, it would be desirable to administer an emesis-inhibiting drug such as a 5-HT_3 antagonist every day until the risk of emesis has substantially subsided. The present class of 5-HT_3 antagonists has not proven especially helpful meeting this need, however, because the 5-HT_3 receptor antagonists currently marketed have proven to be less effective in controlling delayed nausea and vomiting than they are at controlling acute emesis. Sabra, K, *Choice of a 5HT_3 Receptor Antagonist for the Hospital Formulary.* EHP, Oct. 1996;2 (suppl 1):S19-24.

Recently, clinical investigations have been made concerning palonosetron, a new 5-HT_3 receptor antagonist reported in U.S. Patent No. 5,202,333. These investigations have shown that the drug is an order of magnitude more potent than most existing 5-HT_3 receptor antagonists, has a surprising half-life of about 40 hours, and is effective to reduce delayed-onset nausea induced by chemotherapeutic agents. However, formulating palonosetron in liquid formulations has not proven an easy task, typically due to shelf-stability issues. U.S. Pat. No. 5,202,333 discloses an intravenous formulation of palonosetron in example 13 that contains the following ingredients:

Ingredient	Mg
Palonosetron HCI	10-100 mg.
Dextrose Monohydrate	q.s. to make Isotonic
Citric Acid Monohydrate	1.05 mg.
Sodium Hydroxide	0.18 mg.
WFJ	To 1.0 ml.

The formulation has a pH of 3.7 and a shelf stability of less than the 1-2 year time period required by health authorities in various countries.

Ondansetron, its uses, and medicaments made with ondansetron are disclosed in U.S. Patent Numbers 4,695,578, 4,753,789, 4,929,632, 5,240,954, 5,344,658, 5,578,628, 5,578,632, 5,922,749, 5,622,720, 5,955,488, and 6,063,802. Commercially it is distributed by GlaxoSmithKline as Zofran® and is indicated for prevention of postoperative nausea and vomiting (PONV), cancer chemotherapy-induced nausea and vomiting (CINV), and radiotherapy-induced nausea and vomiting (RINV) and it is available as an injection, tablets and solution, and as Zofran ODT® (ondansetron) Orally Disintegrating Tablets.

Granisetron, its uses, and medicaments made with granisetron are disclosed in U.S. Patent Numbers 4,886,808, 4,937,247, 5,034,398 and 6,294,548. Commercially it is

distributed by Roche Laboratories Inc. as Kytril®, indicated for the prevention of nausea and vomiting associated with chemotherapy or radiation therapy, and is offered in tablet form, oral solution, and as an injection.

Alosetron, its uses, and medicaments made with alosetron are disclosed in U.S. Patent Numbers 5,360,800 and 6,284,770. Commercially it is distributed by GlaxoSmithKline as Lotronex®.

Tropisetron is commercially available as Navoban® (Novartis) CAS - 89565-68-4 (tropisetron); CAS - 105826-92-4 (tropisetron hydrochloride) and it is indicated for treatment of PONV and CINV.

Dolasetron, its uses, and medicaments made with ondansetron are disclosed in U.S. Patent Numbers 5,011,846, and 4,906,755. Commercially it is distributed by Aventis Pharmaceuticals Inc. as Anzemet®, indicated for prevention of both PONV and CINV, and it is offered in the form of a tablet or an intravenous solution.

Therefore, there exists a need for a palonosetron formulation with increased stability and thereby increased shelf life. There also exists a need for an appropriate range of concentrations for both the 5-HT_3 receptor antagonist and its pharmaceutically acceptable carriers that would facilitate making a formulation with this increased stability.

It is an object of the present invention to provide a formulation of Palonosetron hydrochloride with increased pharmaceutical stability for preventing and/or reducing emesis.

It is another object of the invention to provide an acceptable range of concentrations which will stabilize a formulation containing Palonosetron hydrochloride.

It is a further object of the invention to provide a formulation of Palonosetron which would allow for prolonged storage.

It is also an object of the invention to provide a formulation of Palonosetron which would allow terminal sterilization.

SUMMARY OF THE INVENTION

The inventors have made a series of discoveries that support a surprisingly effective and versatile formulation for the treatment and prevention of emesis using palonosetron. These formulations are shelf stable for periods greater than 24 months at room temperature, and thus can be stored without refrigeration, and manufactured using non-aseptic, terminal sterilization processes.

In one aspect, the inventors have discovered that formulations which include the active ingredient palonosetron require in some instances only $1/10^{th}$ the amount of other previously known compounds for treating emesis, which surprisingly allows the use of concentrations of palonosetron far below those that would ordinarily be expected. Thus, in one embodiment the invention provides a pharmaceutically stable solution for preventing or reducing emesis comprising a) from about 0.01 mg/mL to about 5 mg/mL palonosetron or a pharmaceutically acceptable salt thereof; and b) a pharmaceutically acceptable carrier.

The inventors have further discovered that by adjusting the formulation's pH and/or excipient concentrations it is possible to increase the stability of palonosetron formulations. Therefore, in another embodiment, the invention provides a pharmaceutically stable solution for preventing or reducing emesis comprising a) palonosetron or a pharmaceutically acceptable salt thereof; and b) a pharmaceutically acceptable carrier, at a pH from about 4.0 to about 6.0. In another embodiment the invention provides a pharmaceutically stable solution for preventing or reducing emesis comprising from about 0.01 to about 5.0 mg/ml palonosetron or a pharmaceutically acceptable salt thereof; from about 10 to about 100 millimoles citrate buffer; and from about 0.005 to about 1.0 mg/ml EDTA.

The inventors have further discovered that the addition of mannitol and a chelating agent can increase the stability of palonosetron formulations. Therefore, in still another embodiment the invention provides a pharmaceutically stable solution for preventing or reducing emesis comprising a) palonosetron or a pharmaceutically

acceptable salt thereof and b) a pharmaceutically acceptable carrier, wherein the pharmaceutically acceptable carrier comprises a chelating agent and mannitol.

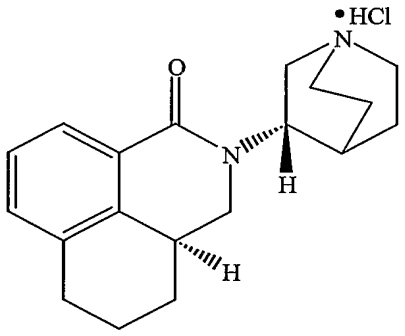
DETAILED DESCRIPTION OF THE INVENTION

DEFINITIONS

"Vial" means a small glass container sealed with the most suitable stopper and seal, other suitable primary containers may be used, for instance, but not limited to, pre-filled syringes. Vial also means a sealed container of medication that is used one time only, and includes breakable and non-breakable glass vials, breakable plastic vials, miniature screw-top jars, and any other type of container of a size capable of holding only one unit dose of palonosetron (typically about 5 mls.).

Throughout this specification the word "comprise," or variations such as "comprises" or "comprising," will be understood to imply the inclusion of a stated element, integer or step, or group of elements, integers or steps, but not the exclusion of any other element, integer or step, or group of elements, integers or steps

"Palonosetron" means (3aS)-2,3,3a,4,5,6-Hexahydro-2-[(S)-1-Azabicyclo[2.2.2]oct-3-yl]2,3,3a,4,5,6-hexahydro-1-oxo-1*H*benz[*de*]isoquinoline, and is preferably present as the monohydrochloride. Palonosetron monohydrochloride can be represented by the following chemical structure:



Concentrations -- When concentrations of palonosetron are given herein, the concentration is measured in terms of the weight of the free base. Concentrations of all other ingredients are given based on the weight of ingredient added to the solution.

"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.

"Pharmaceutically acceptable salts" means salts which are pharmaceutically acceptable, as defined above, and which possess the desired pharmacological activity. Such salts include acid addition salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or with organic acids such as acetic acid, propionic acid, hexanoic acid, heptanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, o-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2,-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid p-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, p-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like.

In addition, pharmaceutically acceptable salts may be formed when an acidic proton present is capable of reacting with inorganic or organic bases. Acceptable inorganic bases include sodium hydroxide, sodium carbonate, potassium hydroxide, aluminum hydroxide and calcium hydroxide. Acceptable organic bases include ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine and the like.

DISCUSSION

The fact that palonosetron can be formulated in some instances at concentrations of only about 1/10th the amount of other previously known compounds for treating emesis, surprisingly allows the use of concentrations of palonosetron far below those that would ordinarily be expected. Thus, in one embodiment the invention provides a pharmaceutically stable solution for preventing or reducing emesis comprising a) from about 0.01 mg/mL to about 5 mg/mL palonosetron or a pharmaceutically acceptable salt thereof; and b) a pharmaceutically acceptable carrier. Similarly, in another embodiment the invention provides a method of formulating a pharmaceutically stable solution of palonosetron comprising admixing from about 0.01 mg/mL to about 5 mg/mL palonosetron or a pharmaceutically acceptable salt thereof; with a pharmaceutically acceptable carrier. In alternative embodiments, the formulation includes palonosetron or a pharmaceutically acceptable salt thereof in a concentration from about 0.02 mg/mL to about 1.0 mg/mL, from about 0.03 mg/mL to about 0.2 mg/mL, and most optimally about 0.05 mg/ml.

A particular advantage associated with the lower dosages of intravenous palonosetron is the ability to administer the drug in a single intravenous bolus over a short, discrete time period. This time period generally extends from about 10 to about 60 seconds, or about 10 to about 40 seconds, and most preferably is about 10 to 30 seconds. In one particular embodiment the palonosetron is supplied in vials that comprise 5 ml. of solution, which equates to about 0.25 mg of palonosetron at a concentration of about 0.05 mg/ml.

The inventors have further discovered that by adjusting the formulation's pH and/or excipient concentrations it is possible to increase the stability of palonosetron formulations. Therefore, in another embodiment, the invention provides a pharmaceutically stable solution for preventing or reducing emesis comprising a) palonosetron or a pharmaceutically acceptable salt thereof; and b) a pharmaceutically acceptable carrier, at a pH from about 4.0 to about 6.0. Similarly, in another embodiment the invention provides a method of formulating a pharmaceutically stable solution of palonosetron comprising admixing a) palonosetron or a pharmaceutically acceptable salt thereof; and b) a pharmaceutically acceptable carrier, at a pH from about 4.0 to about 6.0. In alternative embodiments, the pH is from about 4.5 to about 5.5, and most

optimally about 5.0. There are many examples to those of skill in the art of suitable solutions to adjust the pH of a formulation. Two exemplary solutions are sodium hydroxide and hydrochloric acid solution, either of which could be used to adjust the pH of the formulation.

In another embodiment the invention provides a pharmaceutically stable solution for preventing or reducing emesis comprising from about 0.01 to about 5.0 mg/ml palonosetron or a pharmaceutically acceptable salt thereof and (i) from about 10 to about 100 millimoles citrate buffer, and/or (ii) from about 0.005 to about 1.0 mg/ml EDTA. Similarly, in another embodiment the invention provides a method of formulating a pharmaceutically stable solution of palonosetron comprising admixing from about 0.01 to about 5.0 mg/ml palonosetron or a pharmaceutically acceptable salt thereof and (i) from about 10 to about 100 millimoles citrate buffer, and/or (ii) from about 0.005 to about 1.0 mg/ml EDTA. The citrate buffer can be in the form of citric acid and/or a salt of citric acid such as trisodium citrate. In various embodiments, the ranges of one or more of the foregoing ingredients can be modified as follows:

- The formulation may comprise palonosetron or a pharmaceutically acceptable salt thereof in a concentration from about 0.02 mg/mL to about 1.0 mg/mL, from about 0.03 mg/mL to about 0.2 mg/mL palonosetron hydrochloride, and most optimally about 0.05 mg/ml.

- The formulation may comprise citrate buffer in a concentration of from about 10 to about 40 millimoles, or 15-30 millimoles.

- The formulation may comprise EDTA in a concentration of from about 0.005 mg/ml to about 1.0 mg/ml, or about 0.3 to about 0.7 mg/ml, and most optimally about 0.5 mg/ml.

The inventors have further discovered that the addition of mannitol and a chelating agent can increase the stability of palonosetron formulations. Therefore, in still another embodiment the invention provides a pharmaceutically stable solution for preventing or reducing emesis comprising a) palonosetron or a pharmaceutically acceptable salt thereof and b) a pharmaceutically acceptable carrier, wherein the pharmaceutically acceptable carrier comprises a chelating agent and mannitol. Similarly,

in another embodiment the invention provides a method of formulating a pharmaceutically stable solution of palonosetron comprising admixing a) palonosetron or a pharmaceutically acceptable salt thereof and b) a pharmaceutically acceptable carrier, wherein the pharmaceutically acceptable carrier comprises a chelating agent and mannitol. The chelating agent is preferably EDTA, and, in various embodiments the chelating agent is present in a concentration of from about 0.005 to about 1.0 mg/mL or from about 0.05 mg/mL to about 1.0 mg/mL or from about 0.3 to about 0.7 mg/ml, or most optimally about 0.5 mg/ml. In various embodiments the mannitol is present in a concentration of from about 10.0 mg/ml to about 80.0 mg/ml, from about 20.0 mg/mL to about 60.0 mg/ml, or from about 40.0 to about 45.0 mg/ml.

Injectable formulations are typically formulated as aqueous solutions in which water is the primary excipient. Oral formulations will differ from injectable formulations generally by the additional presence of flavoring agents, coloring agents, or viscosity agents. Natural or synthetic sweeteners include, among others, mannitol, sorbitol, saccharose, saccharine, aspartame, acelsulphame K, or cyclamate. These agents are generally present in concentrations in excess of 100 mg/ml or 250 mg/ml when used as sweetening agents, in contrast to the 41.5 mg/ml concentration of mannitol described in some of the embodiments of the invention, in which mannitol is acting simply as a tonicifying agent.

The formulations of the present invention are particularly suited for use in injectable and oral liquid formulations, but it will be understood that the solutions may have alternative uses. For example, they may be used as intermediates in the preparation of other pharmaceutical dosage forms. Similarly, they may have other routes of administration including intranasal or inhalation. Injectable formulations may take any route including intramuscular, intravenous or subcutaneous.

Still further embodiments relate to improvements in the ease with which the palonosetron formulation can be stored or manufactured. In particular, the inventors have discovered that the formulations of the present invention allow storage of the product for extended periods at room temperature. Thus, in yet another embodiment the invention provides a method of storing one or more containers in which are contained a solution of

palonosetron or a pharmaceutically acceptable salt thereof comprising: a) providing a room comprising said one or more containers; b) adjusting or maintaining the temperature of the room at greater than about ten, 15, or 20 degrees celcius; and c) storing said containers in said room for one month, 3 months, 6 months, one year, 18 months, 24 months or more (but preferably not exceeding 36 months), wherein (i) the palonosetron or pharmaceutical salt thereof is present in a concentration of from about 0.01 mg/mL to about 5.0 mg/mL, (ii) the pH of the solution is from about 4.0 to about 6.0, (iii) the solution comprises from about 0.01 to about 5.0 mg/ml palonosetron or a pharmaceutically acceptable salt thereof, from about 10 to about 100 millimoles citrate buffer and from about 0.005 to about 1.0 mg/ml EDTA, (iv) the solution comprises a chelating agent, or (v) the solution comprises from about 10 to about 100 milliMoles of a citrate buffer.

The stability of the foregoing formulations also lends itself well to terminal sterilization processes in the manufacturing process. Therefore, in still another embodiment the invention provides a method of filling a container in which is contained a solution of palonosetron or a pharmaceutically acceptable salt thereof comprising: a) providing one or more sterile open containers (preferably 5 ml. vials); b) filling said containers with a solution of palonosetron in a non-aseptic environment; c) sealing said filled containers; and d) sterilizing said sealed, filled containers, wherein (i) the palonosetron or pharmaceutical salt thereof is present in a concentration of from about 0.01 mg/mL to about 5 mg/mL, (ii) the pH of the solution is from about 4.0 to about 6.0, (iii) the solution comprises from about 0.01 to about 5.0 mg/ml palonosetron or a pharmaceutically acceptable salt thereof, from about 10 to about 100 millimoles citrate buffer and from about 0.005 to about 1.0 mg/ml EDTA, (iv) the solution comprises a chelating agent, or (v) the solution comprises from about 10 to about 100 milliMoles of a citrate buffer.

EXAMPLES

EXAMPLE 1: STABILIZING PH

A study was conducted to determine the effect of pH on formulations containing palonosetron hydrochloride, measuring the stability at 80°C at pH 2.0, 5.0, 7.4, and 10.0. The results indicated that palonosetron hydrochloride is most stable at pH 5.0.

EXAMPLE 2: STABILIZING CONCENTRATION RANGES

A formulation optimization study was performed using an experimental design software. Twenty-four lots of drug product were analyzed to investigate the appropriate concentration ranges for palonosetron hydrochloride (0.05 mg/mL to 5.0 mg/mL), citrate buffer (0 to 80 mM) and EDTA (0 to 0.10%). The level of EDTA and citrate buffer were selected based on the optimal formulation, which was shown to be formulated with EDTA 0.05% and 20 mM citrate buffer at pH 5.0. The results of this study indicated that palonosetron concentration was also a critical factor in chemical stability, with greatest stability seen at the lowest palonosetron concentrations.

EXAMPLE 3: TONICIFYING AGENT

Formulations of palonosetron hydrochloride in citrate buffer were prepared including either a) sodium chloride or b) mannitol. The palonosetron hydrochloride formulation including mannitol showed superior stability. The optimum level of mannitol required for an isotonic solution was found to be 4.15%.

EXAMPLE 4: FORMULATION I

The following is a representative pharmaceutical formulation containing palonosetron that is useful for intravenous formulations, or other liquid formulations of the drug.

Ingredient	mg/mL
Palonosetron Hydrochloride	0.05*
Mannitol	41.5

EDTA	0.5
Trisodium citrate	3.7
Citric acid	1.56
WFJ	q.s. to 1 ml
Sodium hydroxide solution and/or hydrochloric acid solution	pH 5.0 ± 0.5

* calculated as a free base

EXAMPLE 5: FORMULATION II

The following is a representative pharmaceutical formulation containing palonosetron that is useful for oral formulations, or other liquid formulations of the drug.

Ingredient	mg/mL
Palonosetron Hydrochloride	0.05*
Mannitol	150
EDTA	0.5
Trisodium citrate	3.7
Citric acid	1.56
WFJ	q.s. to 1 ml
Sodium hydroxide solution and/or hydrochloric acid solution	pH 5.0 ± 0.5
Flavoring	q.s.

* calculated as a free base

EXAMPLE 6 -- STABILITY OF PALONOSETRON WITHOUT DEXAMETHASONE

The physical and chemical stability of palonosetron HCl was studies in concentrations of 5 μg/mL and 30 μg/mL in 5% dextrose injection, 0.9% sodium chloride injection, 5% dextrose in 0.45% sodium chloride injection, and dextrose 5% in lactated Ringer's injection. The admixtures were evaluated over 14 days at 4 °C in the dark and for 48 hours at 23 °C under fluorescent light.

Test samples of palonosetron HCl were prepared in polyvinyl chloride (PVC) bags of the infusion solutions at concentrations of 5 and 30 μg/mL. Evaluations for physical and chemical stability were performed on samples taken initially and after 1, 3, 5, 7, and 14 days of storage at 4 °C and after 1, 4, 24, and 48 hours at 23 °C. Physical stability was assessed using visual observation in normal room light and using a high-intensity monodirectional light beam. In addition, turbidity and particle content were measured electronically. Chemical stability of the drug was evaluated by using a stability-indicating high performance liquid chromatographic (HPLC) analytical technique.

All samples were physically stable throughout the study. The solution remained clear, and little or no change in particulate burden and haze level were found. Additionally, little or no loss of palonosetron HCl occurred in any of the samples at either temperature throughout the entire study period.

EXAMPLE 7 -- STABILITY OF PALONOSETRON WITH DEXAMETHASONE

The physical and chemical stability of palonosetron HCl 0.25 mg admixed with dexamethasone (as sodium phosphate) 10 mg or 20 mg in 5% dextrose injection or 0.9% sodium chloride injection in polyvinyl chloride (PVC) minibags, and also admixed with dexamethasone (as sodium phosphate) 3.3 mg in 5% dextrose injection or 0.9% sodium chloride injection in polypropylene syringes at 4 °C in the dark for 14 days and at 23 °C exposed to normal laboratory fluorescent light over 48 hours, was studied.

Test samples of palonosetron HCl 5 μg/mL with dexamethasone (as sodium phosphate) 0.2 mg/mL and also 0.4 mg/mL were prepared in polyvinyl chloride (PVC) minibags of each infusion solution. Additionally, palonosetron HCl 25 μg/mL with dexamethasone (as sodium phosphate) 0.33 mg/mL in each infusion solution were prepared as 10 mL of test solution in 20-mL polypropylene syringes. Evaluations for

physical and chemical stability were performed on samples taken initially and after 1, 3, 7, and 14 days of storage at 4 °C and after 1, 4, 24, and 48 hours at 23 °C. Physical stability was assessed using visual observation in normal room light and using a high-intensity monodirectional light beam. In addition, turbidity and particle content were measured electronically. Chemical stability of the drug was evaluated by using a stability-indicating high performance liquid chromatographic (HPLC) analytical technique.

All samples were physically compatible throughout the study. The solutions remained clear, and little or no change in particulate burden and haze level were found. Additionally, little or no loss of palonosetron HCl and dexamethasone occurred in any of the samples at either temperature throughout the entire study period.

This invention has been described with reference to its preferred embodiments. Variations and modifications of the invention will be obvious to those skilled in the art from the foregoing detailed description of the invention.

CLAIMS

What is claimed is:

1) A pharmaceutically stable solution for preventing or reducing emesis comprising:

   a) from about 0.01 mg/mL to about 5 mg/mL palonosetron or a pharmaceutically acceptable salt thereof; and

   b) a pharmaceutically acceptable carrier.

2) The solution of claim 1 wherein the palonosetron or pharmaceutically acceptable salt thereof is in a concentration from about 0.02 mg/mL to about 1.0 mg/mL.

3) The solution of claim 1 wherein the palonosetron or pharmaceutically acceptable salt thereof is in a concentration from about 0.03 mg/mL to about 0.2 mg/mL.

4) The solution of claim 1 wherein the palonosetron or pharmaceutically acceptable salt thereof is in a concentration of about 0.05 mg/mL.

5) The solution of claim 1 comprising palonosetron hydrochloride.

6) The solution of claim 1 wherein the pH is from about 4.0 to about 6.0.

7) The solution of claim 1 wherein the pH is from about 4.5 to about 5.5.

8) The solution of claim 1 wherein the pharmaceutically acceptable carrier comprises a chelating agent.

9) The solution of claim 1 wherein the pharmaceutically acceptable carrier comprises from about 0.005 mg/ml to about 1.0 mg/ml EDTA.

10) The solution of claim 1 wherein the pharmaceutically acceptable carrier comprises mannitol.

11) The solution of claim 1 wherein the pharmaceutically acceptable carrier comprises from about 10 to about 100 milliMoles of a citrate buffer.

12) The solution of claim 1 adapted for intravenous administration.

13) The solution of claim 1 adapted for oral administration.

14) A pharmaceutically stable solution for preventing or reducing emesis comprising:

a) palonosetron or a pharmaceutically acceptable salt thereof; and

b) a pharmaceutically acceptable carrier,

at a pH from about 4.0 to about 6.0.

15) The solution of claim 14 wherein the pH is from about 4.5 to about 5.5.

16) The solution of claim 14 wherein the pH is about 5.0.

17) The solution of claim 14 wherein the palonosetron or pharmaceutically acceptable salt thereof is in a concentration from about 0.01 mg/mL to about 5.0 mg/mL.

18) The solution of claim 14 wherein the palonosetron or pharmaceutically acceptable salt thereof is in a concentration of about 0.05 mg/mL.

19) The solution of claim 14 wherein the pharmaceutically acceptable carrier comprises a chelating agent.

20) The solution of claim 14 wherein the pharmaceutically acceptable carrier comprises from about 0.005 mg/ml to about 1.0 mg/ml EDTA.

21) The solution of claim 14 wherein the pharmaceutically acceptable carrier comprises mannitol.

22) The solution of claim 14 wherein the pharmaceutically acceptable carrier comprises from about 10 to about 100 milliMoles of a citrate buffer..

23) The solution of claim 14 comprising palonosetron hydrochloride.

24) The solution of claim 14 further comprising sodium hydroxide or hydrochloric acid.

25) The solution of claim 14 adapted for intravenous administration.

26) The solution of claim 14 adapted for oral administration.

27) A pharmaceutically stable solution for preventing or reducing emesis comprising

a) from about 0.01 to about 5.0 mg/ml palonosetron or a pharmaceutically acceptable salt thereof;

b) from about 10 to about 100 millimoles citrate buffer; and

c) from about 0.005 to about 1.0 mg/ml EDTA.

28) The solution of claim 27 comprising about 0.05 mg/ml to of palonosetron hydrochloride.

29) The solution of claim 27 comprising from about 10 to about 40 milliMoles citrate buffer.

30) The solution of claim 27 comprising from about 0.3 to about 0.7 mg/ml of EDTA.

31) The solution of claim 27 adapted for intravenous administration.

32) The solution of claim 27 adapted for oral administration.

33) A pharmaceutically stable solution for preventing or reducing emesis comprising

a) palonosetron or a pharmaceutically acceptable salt thereof and

b) a pharmaceutically acceptable carrier,

wherein the pharmaceutically acceptable carrier comprises a chelating agent.

34) The solution of claim 33 wherein the chelating agent is EDTA.

35) The solution of claim 33 wherein the chelating agent is present in an amount from about 0.005 mg/ml to about 1.0 mg/ml.

36) The solution of claim 33 wherein the chelating agent is present in an amount from about 0.3 mg/ml to about 0.7 mg/ml.

37) The solution of claim 33 wherein the palonosetron or pharmaceutically acceptable salt thereof is in a concentration from about 0.01 mg/mL to about 5.0 mg/mL.

38) The solution of claim 33 wherein the palonosetron or pharmaceutically acceptable salt thereof is in a concentration of about 0.05 mg/mL.

39) The solution of claim 33 wherein the pharmaceutically acceptable carrier comprises mannitol.

40) The solution of claim 33 wherein the pharmaceutically acceptable carrier comprises from about 10 to about 100 milliMoles of a citrate buffer.

41) The solution of claim 33 comprising palonosetron hydrochloride.

42) The solution of claim 33 wherein the pH is from about 4.0 to about 6.0.

43) The solution of claim 33 wherein the pH is from about 4.5 to about 5.5.

44) The solution of claim 33 adapted for intravenous administration.

45) The solution of claim 33 adapted for oral administration.

46) A pharmaceutically stable solution for preventing or reducing emesis comprising

a) palonosetron or a pharmaceutically acceptable salt thereof and

b) a pharmaceutically acceptable carrier,

wherein the pharmaceutically acceptable carrier comprises mannitol.

47) The solution of claim 46 wherein the mannitol is in a concentration from about 10.0 mg/ml to about 80.0 mg/ml.

48) The solution of claim 46 wherein the mannitol is in a concentration from about 40.0 mg/ml to about 45.0 mg/ml.

49) The solution of claim 46 wherein the palonosetron or pharmaceutically acceptable salt thereof is in a concentration from about 0.01 mg/mL to about 5.0 mg/mL.

50) The solution of claim 46 wherein the palonosetron or pharmaceutically acceptable salt thereof is in a concentration of about 0.05 mg/mL.

51) The solution of claim 46 wherein the pharmaceutically acceptable carrier comprises a chelating agent.

52) The solution of claim 46 wherein the pharmaceutically acceptable carrier comprises from about 0.005 mg/ml to about 1.0 mg/ml EDTA.

53) The solution of claim 46 wherein the pharmaceutically acceptable carrier comprises from about 10 to about 100 milliMoles of a citrate buffer.

54) The solution of claim 46 comprising palonosetron hydrochloride.

55) The solution of claim 46 wherein the pH is from about 4.0 to about 6.0.

56) The solution of claim 46 wherein the pH is from about 4.5 to about 5.5.

57) The solution of claim 46 adapted for intravenous administration.

58) The solution of claim 46 adapted for oral administration.

59) A pharmaceutically stable solution for preventing or reducing drug induced emesis comprising

a) palonosetron or a pharmaceutically acceptable salt thereof and

b) a pharmaceutically acceptable carrier,

wherein the pharmaceutically acceptable carrier comprises from about 10 to about 100 milliMoles of a citrate buffer.

60) The solution of claim 59 wherein the pharmaceutically acceptable carrier comprises from about 10 to about 70 milliMoles of a citrate buffer.

61) The solution of claim 59 wherein the pharmaceutically acceptable carrier comprises from about 10 to about 40 milliMoles of a citrate buffer.

62) The solution of claim 59 wherein the palonosetron or pharmaceutically acceptable salt thereof is in a concentration from about 0.01 mg/mL to about 5.0 mg/mL.

63) The solution of claim 59 wherein the palonosetron or pharmaceutically acceptable salt thereof is in a concentration of about 0.05 mg/mL.

64) The solution of claim 59 wherein the pharmaceutically acceptable carrier comprises a chelating agent.

65) The solution of claim 59 wherein the pharmaceutically acceptable carrier comprises from about 0.005 mg/ml to about 1.0 mg/ml EDTA.

66) The solution of claim 59 wherein the pharmaceutically acceptable carrier comprises mannitol.

67) The solution of claim 59 comprising palonosetron hydrochloride.

68) The solution of claim 59 wherein the pH is from about 4.0 to about 6.0.

69) The solution of claim 59 wherein the pH is from about 4.5 to about 5.5.

70) The solution of claim 59 adapted for intravenous administration.

71) The solution of claim 59 adapted for oral administration.

72) A method of storing one or more containers in which are contained a solution of palonosetron or a pharmaceutically acceptable salt thereof comprising:

a) providing a room comprising said one or more containers;

b) adjusting or maintaining the temperature of the room at greater than about ten degrees celcius;

c) storing said containers in said room for one month or more,

wherein (i) the palonosetron or pharmaceutical salt thereof is present in a concentration of from about 0.01 mg/mL to about 5.0 mg/mL, (ii) the pH of the solution is from about 4.0 to about 6.0, (iii) the solution comprises from about 0.01 to about 5.0 mg/ml palonosetron or a pharmaceutically acceptable salt thereof, from about 10 to about 100 millimoles citrate buffer and from about 0.005 to about 1.0 mg/ml EDTA, (iv) the solution comprises mannitol or a chelating agent, or (v) the solution comprises from about 10 to about 100 milliMoles of a citrate buffer.

73) A method of filling a container in which is contained a solution of palonosetron or a pharmaceutically acceptable salt thereof comprising:

a) providing one or more sterile open containers;

b) filling said containers with a solution of palonosetron in a non-aseptic environment

c) sealing said filled containers; and

d) sterilizing said sealed, filled containers,

wherein (i) the palonosetron or pharmaceutical salt thereof is present in a concentration of from about 0.01 mg/mL to about 5.0 mg/mL, (ii) the pH of the solution is from about 4.0 to about 6.0, (iii) the solution comprises from about 0.01 to about 5.0 mg/ml palonosetron or a pharmaceutically acceptable salt thereof, from about 10 to about 100 millimoles citrate buffer and from about 0.005 to about 1.0 mg/ml EDTA, (iv) the solution comprises mannitol or a

chelating agent or mannitol, or (v) the solution comprises from about 10 to about 100 milliMoles of a citrate buffer.

INTERNATIONAL SEARCH REPORT

nal Application No
PCT/EP2004/000888

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/4747 A61K9/08

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)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 202 333 A (BERGER JACOB ET AL) 13 April 1993 (1993-04-13) cited in the application column 28, line 59-68; examples 10,11,13 ---	1,2,13
A	TANG J ET AL: "THE EFFICACY OF RS-25259, A LONG-ACTING SELECTIVE 5-HT3 RECEPTOR ANTAGONIST, FOR PREVENTING POSTOPERATIVE NAUSEA AND VOMITING AFTER HYSTERECTOMY PROCEDURES" ANESTHESIA AND ANALGESIA, WILLIAMS AND WILKINS, BALTIMORE, MD, US, vol. 87, no. 2, 1998, pages 462-467, XP009027884 ISSN: 0003-2999 the whole document ---	
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in 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
21 April 2004	06/05/2004

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, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Tardi, C

Form PCT/ISA/210 (second sheet) (January 2004)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	STACHER G: "PALONOSETRON HELSINN" CURRENT OPINION IN INVESTIGATIONAL DRUGS, CURRENT DRUGS, LONDON, GB, vol. 3, no. 10, October 2002 (2002-10), pages 1502-1507, XP009027887 ISSN: 0967-8298 the whole document	

INTERNATIONAL SEARCH REPORT

ıational application No.
PCT/EP2004/000888

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 14-71
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: 14-71

In view of the large number and also the wording of the claims presently on file, which render it difficult, if not impossible, to determine the matter for which protection is sought, the present application fails to comply with the clarity and conciseness requirements of Article 6 PCT (see also Rule 6.1(a) PCT) to such an extent that a meaningful search is impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear and concise, namely claims 1-13 and 72-73.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

ıal Application No
PCT/EP2004/000888

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5202333 A	13-04-1993	AT 124698 T	15-07-1995
		AU 642178 B2	14-10-1993
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		BR 1100680 A3	08-02-2000
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		EP 0430190 A2	05-06-1991
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(71) Applicant *(for all designated States except US)*: **HELSINN HEALTHCARE S.A.** [CH/CH]; P.O. Box 357, CH-6915 Pambio Noranco (CH).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BARONI, Luigi** [IT/IT]; Via Monte Bianco, 15, 22060 Bregnano, Como (IT). **MACCIOCCHI, Alberto** [CH/CH]; Via Pizzo Ferraro, 6807 Taverne (CH). **BRAGLIA, Enrico** [CH/CH]; Via Pian Scairolo 9, CH-6912 Pazzallo (CH). **BRAGLIA, Riccardo** [CH/CH]; Via Pian Scairolo 9, CH-6912 Pazzallo (CH).

(74) Agent: **FRITSCHE, Rainer**; Association No. 15, Arnulfstr. 25, 80335 München (DE).

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Published:
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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: USE OF PALONOSETRON TREATING POST-OPERATIVE NAUSEA AND VOMITING

(57) Abstract: Methods are provided to treat post-operative nausea and vomiting, as well as emesis generally, with 5-HT_3 receptor antagonists. In particular, the invention discloses methods for reducing post-operative nausea and vomiting and other emetic events with palonosetron.

WO 2004/073714 A1

METHOD OF TREATING POST-OPERATIVE NAUSEA AND VOMITING

FIELD OF THE INVENTION

The present invention discloses methods to treat post-operative nausea and vomiting, as well as emesis generally, with 5-HT_3 receptor antagonists. In particular, the invention discloses methods for reducing post-operative nausea and vomiting and other emetic events with palonosetron.

BACKGROUND OF THE INVENTION

Post-operative nausea and vomiting (PONV) is one the most common consequences of many anesthetic and surgical procedures. PONV can cause serious side effects such as dehydration, electrolyte imbalance, gastric herniation, wound disruption, esophageal tears, and muscular fatigue. Aside from the medical complications, PONV can cause patients to experience anxiety about undergoing further surgery. Because of delayed recovery and discharge, as well as enhanced medical care, PONV adds substantial costs to an already burdened health care system.

Typically, PONV occurs within 24 hours of surgery. At least between 25 and 40% of surgical patients have PONV. PONV has been correlated with age, obesity, type and duration of surgery, duration of general anesthesia, amount of visceral manipulation, early ambulation, use of opiate analgesics postoperative, and pain. The incidence of PONV averages between 20 and 30% across surgery types (Watcha, M.F. and White, P.F. (1992) "Post-Operative narusa nad vomiting: its etiology, treatment and prevention." *Anesthesiology*, 77:162-184), however five general types of surgical procedures (those of the ear, nose, throat; eye; gynecological; gastrointestinal; and cardiovascular) account for approximately 69% of all PONV cases.

No single drug or class of drug is fully effective in controlling PONV. It has been suggested that prophylactic anti-emetic therapy can be more cost-effective

compared with treatment of established symptoms where operations are associated with a high risk of emesis (Watcha MF and Smith I. (1994) "Cost-effectiveness analysis of anti-emetic therapy for ambulatory surgery." *J Clin Anesth*, 6: 370-7).

The number of operations done per year in the Western world and Japan is on the order of 65 million. Many anesthetists and anesthesiologists currently use prophylactic anti-emetics such as low dose metoclopramide (10 mg) pre- or peri-operatively and many use no prophylactic anti-emetics at all due to poor efficacy of current agents coupled with troublesome side-effects such as dystonic reactions and somnolence. Thus the need for a safer and efficacious antiemetic in PONV is present.

PONV is thought to be mediated through serotonin (5 hydroxytryptamine, 5HT) receptors in the gastrointestingal tract, the nucleus solitarius, and the chemoreceptor trigger zone of the area postrema. Contributing factors include the release of 5HT from enterochromaffin cells in the small bowel, which leads to the stimulation of vagal afferent fibers that in turn cause 5HT release in the area postrema and direct chemoreceptor trigger zone stimulation by opiates and anesthetic drugs. Although vestibular stimulation is not mediated through 5HT3 receptors, when it is enhanced by the effects of residual anesthetic drugs it also contributes to PONV.

There are nine groups of agents that are used clinically for the treatment of emesis, including: anticholinergics (e.g. scopolamine), antihistamines (e.g. hydroxyzine, promethazine), phenothiazines, butyrophenones (e.g. droperidol), cannabinoids, benzamides, glucocorticoids, and benzodiazepines (*Merck Manual* (1992) Merck Research Laboratories).

In recent years an additional class of drugs referred to as 5-HT_3 (5-hydroxytryptamine) receptor antagonists has been developed that treat emesis by antagonizing cerebral functions associated with the 5-HT_3 receptor. See "Drugs Acting on 5-Hydroxytryptamine Receptors" (Sep. 23, 1989) *The Lancet* and refs. cited therein. Competitive antagonists of the 5-HT3 receptor are used clinically as antiemetic agents. These agents include: ondansetron (Zofran, GlaxoWelcome), granisetron (Kytril, SmithKline Beecham) and tropisetron (Navoban, Sandoz), and

dolasetron (Anzemet, Aventis). At the present time, the 5-HT3* competitive antagonists in combination with the corticosteroid dexamethasone represent the best prophylaxis and treatment of acute nausea and/or vomiting.

U.S. Patent No. 4,695,578, to Glaxo discloses 1,2,3,9-tetrahydro-3-imidazol-1-ylmethyl-4H-carbazol-4-ones compositions (ondansetron, Zofran), potent selective antagonists of 5-HT receptors, useful in the treatment of migraine and psychotic disorders such as schizophrenia, while U.S. Patent Nos. 4,753,789, 4,929,632, 5,240,954, 5,578,628, 5,578,632, 5,922,749, 5,955,488, and 6,063,802, also to Glaxo, claims these compounds for the relief of nausea and vomiting. Zofran has been approved by the FDA for PONV, however, negative side effects have been noted in postoperative clinical tests. The most common are dizziness, headache, drowsiness, sedation, and constipation. Other adverse effects are diarrhea, dry mouth, and skin rash. Furthermore, the serum half life of ondansetron is on the order of 5.5 hours (*Physicians desk reference* (2002)), therefore treatment of PONV often requires multiple doses. In addition, the dose level can vary widely, depending on physician involvement. Furthermore, it is suggested that Zofran be administered in three 8 mg doses or as a slow intravenous injection (Dupeyron, et al. (1993) "The effect of oral ondansetron in the prevention of postoperative nausea and vomiting after major gynaecological surgery performed under general anesthesia" *Anaesthesia* v48, p214-18 (1993); Sung et al. "A double blind, placebo controlled pilot study examining the effectiveness of intravenous ondansetron in the prevention of postoperative nausea and emesis" *J. Clin Anesth* v5, p22-29 (1993); McKenzie et al. "A randomized, double blind pilot study examining the use of intravenous ondansetron in the prevention of postoperative nausea and vomiting in female inpatients" *J. Clin. Anesth.* V5, p30-36 (1993)).

Kytril (granisetron hydrochloride), a selective blocking agent of the 5-HT_3 receptor is currently used for both the prevention and treatment of PONV. U.S. Patent Nos. 5,952,340, 4,886,808, 4,937,247, 5,034,398 and 6,294,548, to SmithKLine Beecham, filed May 23, 1996 disclose a method of treatment of PONV by

administration of granisetron to surgical patients. The patents state that granisetron can be administered intravenously, either pre-operatively, peri-operatively; or post-operatively. When used for prevention, Kytril is given just before or during surgery to prevent PONV from occurring. In the case of treatment, Kytril is given to a patient who experiences PONV after surgery is completed. However, Kytril can cause headache, constipation, weakness, drowsiness or diarrhea. The plasma half-life of Kytril is also found to be less than a day, ranging from 1.77-17.73 hours.

Dolasetron is used to prevent nausea and vomiting caused by cancer chemotherapy, anesthesia, or surgery. Uses of this compound are detailed in U.S. Patent Nos. 4,906,755 and 5,011,846, directed to a group of esters hexahydro-8-hydroxy-2,6-methano-2H-quinolizin-3(3H)-ones useful in the treatment disorders including drug-induced vomiting, stimulation of gastric motility. Additionally, dolasetron serum half life is only approximately 7.5 hours (*Physicians Desk Reference* (2002)), therefore treatment of PONV could require administration of multiple doses. This is particularly disadvantageous as it can delay discharge of patients and thereby increase patient and insurance costs.

U.S. Patent Nos. 5,627,190, 5,430,040, 5,280,029, 5,137,893, to G. D. Searle & Co., describe imidazopyridines containing meso-azacycle side chains, which act as antagonists of the serotonin 5-HT_3 receptor and can be useful for the treatment of emesis.

Additional 5HT receptor antagonists have been found. For example, Ponchant et al. (1991) "Synthesis of 5-^{125}I-Iodo-Zacopride, A New Probe for 5-HT_3 Receptor Sites," *J. Lab. Cpds. and Radiopharm.*, Vol. XXIX, No. 10, pp. 1147-1155, discloses substituted 3-quinuclidinyl benzamides useful for 5-HT_3 serotonin receptor binding. U.S. Patent Nos. 4,707,484, 5,189,041, 5,202,333, 5,491,148, and 5,492,914 to Syntex, disclose a class of benz[*de*]isoquinolin-1-ones that act as 5-HT_3 receptor antagonists. Species disclosed in the '333 patent include palonosetron. According to this patent, the class of compounds is useful to treat emesis, including emesis from surgical anesthesia, gastrointestinal disorders, anxiety, depressive states, and pain. In

addition, the '333 patent discloses a general dose range for administration that may range from .1ng/kg to 1 mg/kg body weight per day, preferably from 10 to 100,000 ng/kg/day. However, no enabling examples are provided to allow administration of these species for PONV. The Syntex patents do not disclose any specific data for determining a suitable therapeutic regimen such as the potency of the compounds, the serum half life of the compounds, dose response data, or duration of effect.

The introduction of 5-HT_3 receptor competitive antagonists into clinical practice revolutionized the treatment of emesis because these agents are more efficacious and have fewer side-effects than antiemetic agents from the other groups (Markham, A. & Sorkin, E. M. (1993) *Drugs*, 45:931-952). The American Society of Anesthesiologists suggest $5HT_3$ antagonists as the standard treatment and preventative therapy for PONV, used in 74-78% of patients. Each of the currently available 5-HT_3 antagonists suffers from one or more of the following deficiencies which limits its therapeutic utility: potency, duration of effect, window of therapeutic efficacy, ease of dosing, side effects, and certainty of the dosing regimen. Sabra, K (1996) *id.* Although side effects are typically mild to moderate and transient, they include headache, lightheadedness or dizziness, abdominal pain or cramping, constipation, sedation and fatigue, elevations in hepatic transaminases and/or bilirubin, and electrocardiographic changes. (Gregory , RE and Ettinger, DS (1998) "$5HT_3$ receptor antagonists for the prevention of chemotherapy-induced nausea and vomiting. A comparison of their pharmacology and clinical efficacy" *Drugs*, 55(2):173-189.) In addition, these drugs are limited in their efficacy. Specifically, 38-50% of patients require additional therapy after treatment with the most popular 5-HT_3 antagonist, Zofran (Phillip Scuderi et al. (2002) "Single-Dose Oral Ondansetron Prevents Nausea and Vomiting After Inpatient Surgery" *Applied Research*, 1(1)). This is in part due to the short half life and relatively low potency of the drug. The serum half-life of Zofran is approximately 5-6 hours, and typically 3-4 doses must be given to effectively overcome PONV.

5-HT_3 receptor competitive antagonists are currently also very expensive. Consequently, they are not prescribed to the extent that they are needed and the cost of these agents is a burden to the health care system.

One of the greatest challenges in drug dosing is to find a dose that is well-tolerated and consistently efficacious. Finding an optimum dose is complicated by such factors as serum half-life, dosing/efficacy relationships, and, in the case of PONV, the variables inherent in different operative procedures, different anesthetics used, and post-operative treatments required. This challenge is particularly acute when devising single unit dose formulations of the anti-emetic drug that is efficacious over a range of body weights, because single unit dose forms are designed typically to prevent nurses and doctors from titrating the dose in the clinic.

OBJECTS OF THE INVENTION

It is an object of the present invention to provide methods of inhibiting PONV using 5-HT_3 receptor antagonists that have improved potency.

It is an object of the present invention to provide methods of inhibiting PONV using 5-HT_3 receptor antagonists that can be administered at doses that yield fewer incidences of unwanted side effects.

It is a further object of the present invention to provide methods of inhibiting PONV using 5-HT_3 receptor antagonists that can be administered fewer times to reduce the occurrence of unwanted side effects.

It is a further object of the present invention to provide methods of inhibiting PONV using 5-HT_3 receptor antagonists that requires less rescue therapy, potentially reducing the incidence of side effects.

Another object of the present invention is to provide defined doses of palonosetron that can be administered to a patient of nearly any body weight to control PONV.

Still another object of the present invention is to provide 5-HT_3 antagonists that possess increased plasma half-life and prolonged *in vivo* activity.

Another object of the invention is to provide greater flexibility when administering emesis-inhibiting agents before an operation by increasing the size of the window for pretreatment.

Yet another object of the invention is to provide a PONV reducing agent which can be administered orally.

It is a further object of the present invention to provide a PONV reducing agent that can be administered intravenously.

Yet another object of the invention is to provide a PONV reducing agent which can be administered before or after an operation.

Yet another object of the invention is to reduce the cost of PONV therapy.

Still further objects of the invention pertain to the use of palonosetron in the general prevention or treatment of emesis, regardless of the cause.

SUMMARY OF INVENTION

It has surprisingly been discovered that a remarkably small dose of palonosetron is effective against PONV, and that such a small dose is effective for practically the entire time that a patient undergoing a surgical procedure is usually at risk for developing PONV (typically within about 0-36 hours of the operation). Therefore, the invention provides in one embodiment a method of treating or preventing PONV in a human comprising administering from about 0.025 to about 0.25 mg of palonosetron or a pharmaceutically acceptable salt thereof substantially at the time of an operation. The method is effective against PONV caused by a variety of surgical procedures and anesthetic compounds, as discussed in greater detail below.

Another embodiment derives from the unexpectedly long duration of action of palonosetron, and the ability of the compound to prevent "delayed-onset" PONV (i.e. PONV occurring greater than about 4, 6, 8, 12, or 18 hours after surgery). Thus, in another embodiment the invention provides a method of treating or preventing delayed-onset PONV comprising administering a treatment effective amount of

palonosetron or a pharmaceutically acceptable salt thereof substantially at the time of an operation.

Another embodiment derives from the unexpectedly rapid onset of palonosetron following administration, and its use as a rescue medication when PONV is unexpectedly experienced. Thus, in yet another embodiment the invention provides a method of rescuing a patient from PONV comprising administering a treatment effective amount of palonosetron or pharmaceutically acceptable salt thereof shortly after the onset of said PONV. The method will typically be performed greater than about 1, 2, 3, 4, 5, or 6 hours after the operation, but within about 36 hours after the operation.

The surprising potency and the extended plasma half-life of palonosetron also satisfy a number of unmet clinical needs including: increased efficacy, decreased cost, decreased side effects and increased duration of action. Thus, in yet another embodiment the invention provides a method of treating or preventing emesis (regardless of the cause) comprising administering a single treatment effective dose of palonosetron or pharmaceutically acceptable salt thereof during a seven day period beginning substantially from an emesis inducing event. The emesis can be induced by any number of medical procedures, including chemotherapy, radiotherapy, and surgical operations.

Palonosetron has also surprisingly been found to exhibit an efficacy plateau, which when combined with its safety profile allows for a single dose to be effectively administered across a range of body weights. Thus, in another embodiment the invention provides a method of treating or preventing emesis (regardless of its cause) comprising administering a defined dose of palonosetron or a pharmaceutically acceptable salt thereof to a plurality of patients ranging in weight from about 50 to about 80 kilograms, wherein said defined dose is the same among said plurality of patients.

DETAILED DESCRIPTION

Definitions

"Vial" means a small glass container sealed with the most suitable stopper and seal, other suitable primary containers may be used, for instance, but not limited to, pre-filled syringes. Vial also means a sealed container of medication that is used one time only, and includes breakable and non-breakable glass vials, breakable plastic vials, miniature screw-top jars, and any other type of container of a size capable of holding only one unit dose of palonosetron (typically about 5 mls.).

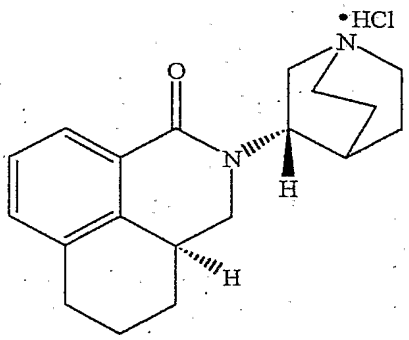
Throughout this specification the word "comprise," or variations such as "comprises" or "comprising," will be understood to imply the inclusion of a stated element, integer or step, or group of elements, integers or steps, but not the exclusion of any other element, integer or step, or group of elements, integers or steps

"PONV" includes any episodes of emesis in the 4 day period following an operation.

"Operation" is any medical procedure during which surgery is performed or general anesthetics are administered to a patient.

"Emesis", for the purposes of this application, will have a meaning that is broader than the normal, dictionary definition and includes not only vomiting, but also nausea and retching.

"Palonosetron" means (3aS)-2,3,3a,4,5,6-Hexahydro-2-[(S)-1-Azabicyclo[2.2.2]oct-3-yl]2,3,3a,4,5,6-hexahydro-1-oxo-1*H*benz[*de*]isoquinoline, and is, in one embodiment, present as the monohydrochloride. Palonosetron monohydrochloride can be represented by the following chemical structure:



"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.

"Pharmaceutically acceptable salts" means salts which are pharmaceutically acceptable, as defined above, and which possess the desired pharmacological activity. Such salts include acid addition salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or with organic acids such as acetic acid, propionic acid, hexanoic acid, heptanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, o-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2,-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid p-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, p-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like.

In addition, pharmaceutically acceptable salts may be formed when an acidic proton present is capable of reacting with inorganic or organic bases. Acceptable inorganic bases include sodium hydroxide, sodium carbonate, potassium hydroxide, aluminum hydroxide and calcium hydroxide. Acceptable organic bases include ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine and the like.

Methods of Administration

One embodiment of the present invention is premised upon the discovery that palonosetron is surprisingly more potent than other 5-HT_3 antagonists in its ability to treat emesis due to an operation. This emesis may be caused either by a surgical procedure or be due to the administration of an anesthetic compound during such an operative procedure. Thus, in one embodiment, the invention provides a method of treating or preventing PONV in a human comprising administering from about 0.025 to about 0.25 mg of a treatment-effective amount of palonosetron or a pharmaceutically acceptable salt thereof substantially at the time of an operation. In one embodiment, the drug is administered substantially at the time of the operation (i.e. in a window of within about 1, 1.5, 2 or 4 hours before the operation, to within about 1, 1.5, 2 or 4 hours after the operation, or during the operation). Administration during an operation can occur, for example, intravenously after skin closure but before leaving the operating room. In another embodiment, this dose is administered after an operation, during recovery, such as within about 48, 24, 12, 8 or 6 hours of an operation. The method can be performed in a single administration of the drug, and can be unaccompanied by further administrations of palonosetron, palonosetron derivatives, or other rescue medications during the period in which PONV from an operation is a risk.

Another embodiment derives from the unexpectedly long duration of action of palonosetron, and the ability of the compound to prevent delayed-onset PONV (i.e. PONV occurring greater than about 4, 6, 8, 12, or 18 hours after surgery, but typically

within about 36 hours of surgery). Thus, in another embodiment the invention provides a method of treating or preventing delayed-onset post-operative nausea and vomiting (PONV) comprising administering a treatment effective amount of palonosetron or a pharmaceutically acceptable salt thereof substantially at the time of an operation.

Another embodiment derives from the unexpectedly rapid effect of palonosetron, and its use as a rescue medication when PONV is unexpectedly experienced. Thus, in yet another embodiment the invention provides a method of rescuing a patient from the onset of PONV comprising administering a treatment effective amount of palonosetron or pharmaceutically acceptable salt thereof shortly after the onset of said PONV (i.e. within about one hour, 30 minutes, or 15 minutes of the onset of PONV) following an operation.

Based upon the surprising potency and extended plasma half-life of palonosetron the invention also provides methods that are generally applicable to any emesis inducing event, including operations, chemotherapy, and radiotherapy. Thus, in yet another embodiment the invention provides a method of treating or preventing emesis comprising administering a single treatment effective dose of palonosetron or pharmaceutically acceptable salt thereof during a seven day period beginning substantially from an emesis inducing event.

Based upon the surprising efficacy plateau and safety profile of palonosetron, methods have been developed in which a single dose is administered across a range of body weights. Thus, in yet another embodiment the invention provides a method of treating or preventing emesis (regardless of its cause) comprising administering a defined dose of palonosetron or a pharmaceutically acceptable salt thereof to a plurality of patients ranging in weight from about 50 to about 80 kilograms, wherein said defined dose is the same among said plurality of patients. A plurality means more than one. It will be understood, however, that a doctor may treat more than 5 or even 10 patients during a busy period of time, and that the number of patients (and doses of palonosetron administered) will vary from doctor to doctor. Said period of

time is not important to the invention, but may be one day, seven days, or even 30 days during which said doctor may treat greater than 5, 10 or even 20 patients with a single dose of palonosetron.

Dosing

The inventors have determined that a single dose of palonosetron generally ranging from about 0.1 to about 100 microgram/kilogram of body weight is effective in the foregoing methods, and that the particular dose will vary depending upon the cause of the emesis. For PONV, doses ranging from about 0.2 to about 30 μg/kg, from about 0.3 to about 10 μg/kg, or from about 0.3 to about 1.0 μg/kg, are generally suitable, as are specific doses of about 0.3, 0.65 and 1.0 μg/kg. A particularly effective dose for PONV regardless of the patient's body weight has been found to range generally from about 0.001 to about 1.0 mg, from about 0.01 to about 0.1 mg., or from about 0.025 to about 0.075 mg of palonosetron. Specfic doses with which the invention can be practiced against PONV include about 0.025, 0.050, 0.075, 0.1, 0.2, and 0.25 mg of palonosetron.

For emesis induced by chemotherapy or radiotherapy, suitable doses have been found to range from about 1 to about 1000 μg/kg, from about 1 to about 100 μg/kg, and from about 3 to about 10 μg/kg based on the body weight of the recipient. A particularly effective dose regardless of the patient's body weight has been found to range from about 0.1 mg to about 1.0 mg of palonosetron. Specific doses with which the invention can be practiced against emesis induced by chemotherapy or radiotherapy are about 0.1 mg, 0.25 mg, 0.5 mg., 0.75 mg. and 1.0 mg. of palonosetron.

It has surprisingly been discovered that the clinical response substantially plateaus at about 1 microgram/ kilogram of body weight. Therefore, efficacy can be expected over a wide range of patient body weights when utilizing doses approximating this amount. These doses can be administered intravenously or orally,

and when administered orally may be administered as a liquid, solid or soft gel capsule.

Another particular advantage associated with the lower dosages of palonosetron is the ability to administer the drug in a single intravenous bolus over a short, discrete time period. This time period generally extends from about 10 to about 60 seconds, or about 10 to about 40 seconds, or about 10 to 30 seconds.

The methods of the present invention can be practiced with mammals other than humans, employing substantially the same dosages when based upon the weight of the animal.

Associated medications and procedures

The inventors have shown that palonosetron is effective against PONV initiated by a variety of surgical procedures. In addition, they have shown that palonosetron is effective against PONV induced by a number of anesthetic compounds.

Operations that can be performed to induce PONV can include any operation, including those with high likelihood of inducing PONV. These can include, but are not limited to surgical procedures including gynecologic procedures, including abdominal or vaginal hysterectomy; abdominal and gastrointestinal procedures and bowel manipulation. Procedures can also include laparoscopic surgical procedures, ear nose and throat procedures, and ophthalmic procedures.

The duration of an operation is a major factor in the development of PONV. Extended surgical procedures are more likely to lead to PONV than shorter operations. Compounds of slow onset must be given before an operation, to ensure that they are effective within a reasonable time after the operation. On the other hand, compounds with rapid onset typically show a short duration of action, and thus cannot be given to a patient before a lengthy procedure. Because it shows a rapid onset, palonosetron can be administered after surgical procedures of any length. At the same time, due to the extended half-life of palonosetron in the body and its

limited side-effects, palonosetron can also be administered before an operation, including operations that are time consuming. In particular, one advantage of palonosetron is that it can be administered before exploratory operations which may lead to lengthy procedures that cannot be forecast with accuracy. Thus, in one embodiment, palonosetron or a pharmaceutically acceptable salt or prodrug thereof is delivered before exploratory surgery. In a subembodiment, the drug is delivered about 1, 1.5, or 2 hours before surgery. In another embodiment, the drug is delivered less than one hour before surgery, for example 10, 20, 30, or 45 minutes before surgery.

Certain anesthetic agents have been associated with a higher incidence of PONV than others. Certain types of premedication, use of opioid analgesics, nitrous oxide, some inhalation agents, and greater depth of anaesthesia can all affect the incidence of PONV. For the purposes of this invention, any type of anesthestic can be utilized. These include, but are not limited to thiopental, nitrous oxide, isoflurane, enflurane, fentanyl, sufentanil, morphine, meperidine, hydromorphone, or narcotic antagonists, vecuronium, succinylcholine, or tubocuararine alone or any combination thereof. Anesthetics also include schedule II narcotics such as: opium, morphine, methadone and codeine, 1-Diphenyl-propane-carboxylic acid, 2-Methyl-3-morpholino-1, 4-Cyano-2-Dimethylamino-4, 4-Diphenyl butane, Alphaprodine HCl—(Nisentel), Anileridine, Benzitramide, Codeine, Dihydrocodeine, Diphenoxylate, Ethylmorphine, Etorphine Hydrochloride, Fentanyl, Granulated Opium, Hydrocodone, Hydromorphone (Dilaudid), Isomethadone, Levo-alphacetylmethadol (LAMM), Levomethorphan, Levorphanol (Levo-Dromoran), Merperidine (Demeral, Pethadol), Metazocine, Methadone (Dolophine), Methadone Intermediate, Metapon, Moramide Intermediate, Morphine, Opium fluid, Opium Extracts, Opium Tincture, Oxycodone , Oxymorphone (Numorphan), Pantopon (Hydrochloride, opium alkaloids), Pethidine, Pethidine-Intermediate-A,4 cyano-1-methyl-4-phenylpiperdine, Pethidine-Intermediate-B ethyl-4-phenylpiperdine-4-carboxylate, Pethidine-Intermediate-C 1-methyl-4-phenylpiperidine-4-carboxylic

acid, Phenazocine, Piminodine, Poppy Straw, Powdered Opium, Racemethorphan, Racemorphan, Raw Opium, Remifentanil, Raw Opium Extracts, Thebaine. Additionally, combinations such as: Oxycodone & Acetaminophen tablets, Oxycodone HCl, Oxycodone Terephthalate & Aspirin tablets, Oxycodone with Acetaminophen, Oxycodone with Aspirin tablets, Percodan-Demi tablets, Percodan tablets, Tylox Capsules. Hallucinogenic substances such as: 1-Dronabinol (some other names for dronabinol: [6aR-trans]-6a,7,8, or (-) delta-9-[trans]-tetrahydrocannabinol 2-Nabilone (another name for Nabilone): [+]-trans-3-(1,1-deimethylheptyl)-6,6a,7,8,10,10a-hexahydro-1-hydroxy-6,6-dimethyl-9H-dibenzo [b,d]pyran-9-one. Opiates such as: Alfentanil, Bulk Dextropropoxyphene (non-dosage form), Carfentanil, Sufentanil. Stimulants such as: Adderall, Coca Leaves, Cocaine, Dextroamphetamine, Ecgonine, Methamphetamine, Methylphenidate, Phenmetrazine. Depressants such as: Amobarbita (Amytal), Amobarbital + Secobarbital (Tuinal), Glutethimide (Doredin), Pentobarbital (Nembutal), Secobarbital (Seconal), 1-Any drug approved by the United States Food and Drug Administration for marketing only as a suppository including Amobarbital, Pentobarbital or Secobarbital shall be in Schedule 11, 2-Immediate Precursors. A material, compound, mixture or preparation which contains a quantity of the following: immediate precursors to amphetamine and methamphetamine; Phenyl-2-propanone, P2P, Benzyl methyl ketoneMethyl benzyl ketone, immediate precursors to phencyclidine, 1-phenycyclohexylamine, 1-piperidineocyclohexaneecarbonitrile pcc. Additional administration of the schedule III drugs such as: Aspirin with Codeine, Codimal PH, Empirin with Codeine, Fioricet with Codeine, Fiorinal with Codeine, Hycodan tablets, Nalline, Nucofed, Nucofed Experctorant Syrup with Codeine, Phenaphen with Codeine, Talwin; Pentazocine, all forms including its salts, Tylenol with Codeine No. 1, 2, 3, and 4, Vanex-HD Liquid, Bancap, Codamine, Codiclear DH Syrup, Codimal PH Syrup, Co-Gesic tablets, Detussin, various, Duocet, Entuss D Liquid, Hitussin Ed Tuss HC liquid, Hycodan, Hycomine, Hycomine Pediatric Syrup, Hycotuss Expectorant, Hydrocodone Compound Syrup, Hydropane, Hydrophen, Hy-Phen Tablets, Lorcet, Lortab, Rolatuss

with Hydrocodone, S. T. Forte. S. T. Forte Liquid 2, Triaminic Expectorant DH, Tussaminic DH Forte, Tussanil DH Syrup, Tussionex, Vanex-HD, Paragoric, Benzphetamine, Chlorphentermine, Chlortermine, Phendimetrazine to include but not necessarily be limited to: Adipost, Adipex-P, Anorex ,Bontril PDM, Melfiat, Melfiat - 105 Unicells, Metra, Obalan, Obezine, Parzine, Phendiet, Phendiet 105, Plegine, Prelu-2, PT 105, Rexigen Forte, Wehless, Wehless-105 Timecells. In addition: Methamphetamine HCl, Conjugated Estrogen, Methyltestosterone, any material, compound, mixture, or preparation containing amobarbital, secobarbital, pentobarbital, or any of their salts and one or more active medicinal ingredients that is not a controlled substance. Any suppository form that contains amobarbital, secobarbital or pentobarbital approved only for use in suppository form. Any substance which contains any quantity of a derivative of chlorhexadol, glutethimide, lysergic acid, lysergic acid amide, methylprylon, sulfondiethylmethane, sulfonethylmethane, sulfone methane. Tiletamine and zolazepam or any of their salts, Other names for tiletamine are: 2-(ethylamino)-2-(2-thienyl)-cyclohexanone, Other names for Zolazepam are: 4-(2-flurophenyl)-6,8-dihydro-1,3,8-trimethylpyrazolo-(3,4-e)(1,4)diazepin-7(1H)-one, flupyrazpon, Butabarbital—Butisol, Chloral Hydrate, Mephobarbital, Metharbital, Methytprylon, Phenobaribtal, Sulfomethane, Sulfondiethylmethane, Sulfonethylmethane, and Talbutal.

It has also been found that the duration in which a patient is anesthetized is correlated to the likelihood that the patient will experience PONV. Thus, in various embodiments, anesthesia is administered to the patient for 1-12 hours, 1-8 hours, 1-6 hours, or 1-4 hours.

In another embodiment the palonosetron is administered in the presence or absence of a steroid such as dexamethasone.

Pharmaceutical Compositions

Although the foregoing discussion has focused upon intravenous and oral administration of palonosetron or pharmaceutically acceptable salts or prodrugs

thereof, the methods of the present invention can be performed by administering the active material by any appropriate route, for example, orally, parenterally, intravenously, intradermally, intramuscularly, transdermally, intranasally, subcutaneously or topically, by suppository in liquid or solid form.

A particularly surprising advantage of the lower dosages required of palonosetron derives from the fact that the stability of palonosetron increases in solution as its concentration decreases. The potency of palonosetron thus allows the palonosetron to be formulated in stable compositions comprising a wide range of concentrations. In one embodiment, the composition is a liquid formulation in which the palonosetron is present as a concentration of from about 0.01 to about 5 mg/ml, from about 0.02 to about 1.0 mg/ml, or from about 0.03 to about 0.2 mg/ml. In one particular embodiment the palonosetron is present in a liquid formulation at a concentration of about 0.05 mg/ml.

The pH of oral solutions of palonosetron suitably ranges from about 4 to about 6, and may suitably be about 5.

In one particular embodiment the palonosetron is supplied in a single unit dose vial, such as for intravenous administration, comprising from about 0.1 to about 10.0 ml, or about 0.5, 1.0 or 1.5 ml, of solution. In one embodiment, the vial includes about 0.025, 0.05, 0.075 or 0.1 mg of palonosetron at a concentration of about 0.05 mg/ml.

The enhanced stability allows the palonosetron to be stored for extended periods of time, exceeding about 1 month, 3 months, 6 months, 1 year, 18 months, or 2 years, but preferably not extending beyond 36 months. This enhanced stability is seen in a variety of storage conditions, including at room temperature.

The compound can be administered as a component of an elixir, suspension, syrup, wafer, 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.

Solid oral compositions will generally include an inert diluent or an edible carrier. They may be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, 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.

Solutions or suspensions used for parenteral, intradermal, subcutaneous, or topical application 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 or dextrose. If administered intravenously, preferred carriers are physiological saline or phosphate buffered saline (PBS).

EXAMPLES

EXAMPLE 1. PREVENTIONOF PONV USING A SINGLE INTRAVENOUS DOSE OF PALONOSETRON

A study was conducted to test the efficacy and safety of five doses of intravenously administered palonosetron for the prophylaxis of postoperative vomiting and nausea. A total of 381 women, 24-80 years of age, scheduled for abdominal or vaginal hysterectomy and having ASA physical status rating of I or II were enrolled in this study. All patients received balanced general anesthesia, including N_2O plus an opiate. Study medication, palonosetron, was administered over 30 seconds through a peripheral IV line at skin closure at the conclusion of the surgical procedure.

Table 1: 24 Hours After Recovery – IV (Evaluable patients)

	Placebo o (n=62)	0.1 µg/kg (n=47)	0.3 µg/kg (n=67)	1.0 µg/kg (n=62)	3.0 µg/kg (n=67)	30 µg/kg (n=67)
% with CR*	19%	34%	34%	44%	30%	45%
p.Value[a]	-	N/A[b]	0.051	0.004	0.174	0.002
% with CC**	19%	34%	33%	44%	30%	45%
p-Value[a]	--	N/A[b]	0.075	0.004	0.174	0.002
Time to Failure (hr) (median)***	3.3	6.0	9.6	19.5	7.3	15.0
p-Value[a]	--	N/A[b]	0.005	< 0.001	0.040	0.002
% no EE§	47%	55%	60%	73%	61%	76%
p-value[a]			0.137	0.003	0.101	< 0.001

* Complete response (CR): The proportion of patients who completed the 24-hour postrecovery observation period without experiencing an emetic episode and without receiving rescue antiemetic therapy.

** Complete control (CC): The proportion of patients who had a complete response and only mild or no nausea

*** Median time (hours) to treatment failure (time to failure): Either emesis or administration of rescue medication, whichever occurred first

§ no emetic episode, no rescue therapy
[a] p-value for treatment effect versus placebo; [b] N/A = not analyzed

Onset and Duration of Antiemetic Activity

Within the first 4 hours of recovery, between 66% and 72% of the evaluable patients treated with palonosetron 0.3-30 μg/kg had a complete response, compared with 48% of placebo-treated patients (30/62). The 0.3-, 1-, and 30-μg/kg dose groups were statistically significantly superior to placebo (p = 0.008-0.035), whereas the 3-μg/kg dose group was nearly significantly different (p 0.059). In addition, 57% of the 0.1-μg/kg-treated patients (27/47) had a complete response.

Over this same time period, statistically significantly more patients in the 0.3-, 1-, and 30-μg/kg treatment groups were free from emetic episodes compared with the placebo group (90-94% vs. 73%; p = < 0.001--0.015), whereas there was no difference between the 0.1- and 3-μg/kg dose groups versus placebo.

Table 2: 4 Hours After Recovery - IV

	Placebo (n = 62)	0.1 μg/kg (n = 47)	0.3 μg/kg (n = 67)	1 μg/kg (n = 62)	3 μg/kg (n = 67)	30 μg/kg (n = 67)
% with CR p-value[a]	48%	57%	72% 0.008	69% 0.023	66% 0.059	66% 0.035
% no EE p-value[a]	73%	68%	90% 0.015	92% 0:005	78% 0.568	94% < 0.001

[a] p-Value for treatment effect versus placebo

Two hours postrecovery, 24.2% of placebo-treated patients (15/62) experienced an emetic episode, compared with 4.5% (3/67), 6.5% (4/62), and 10.4% (7/67) of patients .in the 30-μg/kg, 1-μg/kg, and 0.3-μg/kg treatment groups respectively. At 12 hours, 13.4% (9/67), 14.5% (9/62), 29.9% (20/67), end 45.2% (28/62) of 30-μg/kg--, 1-μg/kg-, 0.3-μg/kg-, and placebo-treated patients experienced one or more emetic episodes.

Rescue Medication

The "failure rate" for patients experiencing emetic episodes between Hours 12 and 24 decreased relative to the first 12 post-recovery hours. At 24 hours, 23.9% (16/67), 27.4% (17/62), 40.3% (27/67), and 53.2% (33/62) of 30-μg/kg-, 1-μg/kg-, 0.3-μg/kg-, and placebo-treated patients had experienced an emetic episode. Approximately 40% of evaluable placebo-treated patients (25/62, 40.3%) received rescue therapy within the first 2 hours, compared with approximately 21-31% of palonosetron-treated patients. At 8 hours, 62.9% of placebo-treated patients (39/62) received rescue medication, compared with 35.5-50.7% of palonosetron-treated patients. By 24 hours, more than three-quarters of placebo-treated patients (48/62, 77.4%) had received rescue therapy, compared with 50.7% (34/67) and 51.6% (32762) of palonosetron 30-μg/kg- and 1 μg/kg-treated patients, respectively, and 59.6% (28/47) and 59.7% (40/67) of palonosetron 0.1-μg/kg- and 0.3-μg/kg--treated patients, respectively.

Table 3: Duration of Effect (hours) - IV

	Placebo (n = 62)	0.1μg/kg (n = 47)	0.3μg/kg (n = 67)	1 μg/kg (n = 62)	3 μg/kg (n = 67)	30 μg/kg (n = 67)
Emetic Episode (25th Percentile)	2.3 16.3	2.2 > 24	8.4 > 24	21.8 > 24	4.9 > 24	> 24 > 24
Rescue (50th percentile)	4.3	8.5	9.9	21.3	8.0	23.2
Time to Failure (50th percentile)	3.3	6.0	9.6	19.5	7.3	15.0

Control of Nausea

Evaluable patients who received palonosetron 1 μg/kg, 3 μg/kg, and 30 μg/kg reported statistically significantly less nausea over the 24-hour period following recovery than those who received placebo. Nearly half of patients (32/67, 47:8%) who received 30 μg/kg reported no nausea, and no patients reported severe nausea. By comparison, 11.7% of placebo-treated patients (7/60) reported severe nausea and only 23.3% (14/60) reported no nausea (p-value for 30 μg/kg vs. placebo = 0.001). Only 2 patients each in the 1 μg/kg (2/61, 3.3%) and 3 μg/kg groups (2/66, 3.0%) reported severe nausea, whereas 36.1% (22/61) and 34.8% (23/66) reported no nausea, respectively (p-value for 1 μg/kg vs. placebo = 0.009; p-value for 3 μg/kg vs. placebo = 0.049).

Table 4: Nausea During 24 Hours After Recovery - IV

	Placebo (n = 62)	1 μg/kg (n - 62)	3 μg/kg (n = 67)	30 μg/kg (n = 67)
No Nausea	23.3%	36.1%	34.8%	47.8
Severe Nausea	11/7%	3.3%	3.0%	0.0%
Mean Score	1.22	0.82	0.92	0.66
p-value vs. Placebo	---	0.009	0.049	0.001

EXAMPLE 2. ORAL ADMINISTRATION OF PALONOSETRON TO TREAT PONV

A study was performed to test the efficacy, safety, and pharmacokinetics of five doses of orally administered palonosetron for the prophylaxis of postoperative vomiting and nausea. Three hundred fifty-one patients, 308 women and 43 men, 19-75 years of age, scheduled for elective laparoscopic surgical procedures and having an ASA physical status rating of I and II were enrolled in this study. All patients received balanced general anesthesia, including NO2 plus an opiate.

Doses of palonosetron were calculated based on the patient's body weight at the screening visit, rounded to the nearest kilogram. Each dose was diluted to a total volume of 25 mL by adding sterile water to the dosing cup. The dosing cup was rinsed with 25 mL of sterile water and the patient also swallowed this 25 mL. Study medication was administered 2 hours prior to scheduled induction of anesthesia for surgeries requiring nasogastric suction and 1 hour prior to scheduled induction of anesthesia for all other laparoscopic surgical procedures.

Orally-administered palonosetron reached a plateau with respect to clinical response at a dose of 1 μg/kg. At this dose, it was generally more effective than placebo and as effective as the higher doses of palonosetron.

Twenty-Four-Hour Results

Statistically significant differences between palonosetron and placebo were observed at three dose levels of palonosetron (1, 10, and 30 μg/kg) and a near-significant difference for 3.0-μg/kg-treated patients ($p = 0.059$) with respect to the primary efficacy variable, the proportion of patients with a complete response, that is, the proportion of patients who completed the 24-hour postrecovery observation period without experiencing an emetic episode and without receiving rescue antiemetic therapy. At the 1, 10, and 30 μg/kg dose levels, 58%, 59%, and 53% of the patients, respectively, treated with palonosetron ($p < 0.018$) had a complete response as compared with 33% of placebo-treated patients. The more conservative intent-to-treat analysis of the complete response variable also demonstrated statistically significant differences for patients treated with 1, 3, 10, and 30 μg/kg.

Table 5: 24 Hours After Recovery (Evaluable Patients) - oral administration						
	Placebo (n = 62)	0.3 µg/kg (n = 30)	1 µg/kg (n = 57)	3 µg/kg (n = 54)	10 µg/kg (n = 49)	30 µg/kg (n = 67)
% with CR p-value[a]	33%	37%	58% 0.013	52% 0.059	59% 0.009	53% 0.018
% with CC p-value[a]	33%	37%	58% 0.013	52% 0.059	57% 0.016	51% 0.038
% no EE p-value[a]	40%	50%	67% 0.007	63% 0.019	71% 0.001	65% 0.008

complete response (CR), complete control (CC), and no emetic episodes (EE) for the six dose groups

[a] p-value for treatment effect versus placebo

Onset and Duration of Antiemetic Activity

Within the first 4 hours of recovery, between 61% and 76% of the evaluable patients treated with palonosetron 1-30 µg/kg had a complete response, compared with 56% of placebo-treated patients (32/57). Only the 10-µg/kg dose was statistically significantly superior to placebo (p = 0.04). Over this same time period, statistically significantly more patients in the 3 and 10 µg/kg treatment groups were free from emetic episodes, compared with the placebo group (81% and 82% vs. 63%; p -< 0.043), whereas there was no difference among the 1.0- and 30-µg/kg and placebo treatment groups (72% and 69% vs. 63%).

Table 6: 4 Hours After Recovery (Evaluable Patients) – oral						
	Placebo (n = 62)	0.1 µg/kg (n = 47)	0.3 µg/kg (n = 67)	1 µg/kg (n = 62)	3 µg/kg (n = 67)	30 µg/kg (n = 67)
% with CR p-value[a]	56%	60%	61% 0.656	70% 0.149	76% 0.04	63% 0.238
% no EE p-value[a]	63%	73%	72% 0.367	81% 0.043	82% 0.043	69% 0.307

[a] p-value for treatment effect versus placebo

Control of Nausea

Patients who received palonosetron 1, 3, 10, and 30 μg/kg reported statistically significantly less nausea over the 24-hour period following recovery than those who received placebo. Approximately half of patients (44.8%-55.8%) who received palonosetron 1-30 μg/kg reported no nausea, and 2.2%-7.7% of patients reported severe nausea. By comparison, 10.5% of placebo-treated patients (6/57) reported severe nausea and 31.6% (18157) reported no nausea (p-value vs. placebo <; 0.015). The palonosetron 0.3 μg/kg treatment group was intermediate to the placebo group and the other palonosetron treatment groups.

Table 7: Nausea During 24 Hours After Recovery – oral

	Placebo (n = 62)	0.3 μg/kg (n - 29)	1 μg/kg (n = 53)	3 μg/kg (n = 52)	10 μg/kg (n = 45)	30 μg/kg (n = 58)
No Nausea	31.6%	44.8%	52.8%	55.8%	51.1%	44.8%
Severe Nausea	10.5%	3.4%	3.8%	7.7%	2.2%	5.2%
Mean Score	1.0	0.83	0.64	0.65	0.71	0.79
p-value vs. Placebo		N/A	0.012	0.015	0.012	0.007

Rescue Antiemetics

Promethazine (Phenergan®) and droperidol (Inapsine®) were the most frequently used rescue antiemetics, administered to 15.1% and 13.1% of patients, respectively. Other antiemetics administered were metoclopramide (Reglan®, 8.8%) proclorperazine (Compazine®, 4.8%), scopolamine (Transderm Scop®, 2,0%), and trimethobenzamide (Tigan®, 0.3%). Four patients (1.1%) received ondansetron although the protocol stated that patients should not be rescued with 5-HT_3 receptor antagonists.

EXAMPLE 3. INTRAVENOUS FORMULATION

Table 8 below presents a representative formulation of palonosetron formulated for intravenous administration.

Table 8: Representative IV Formulation	
Ingredient	**Weight Parts (mg/ml)**
Palonosetron Hydrochloride	0.05
Mannitol	41.5
EDTA	0.5
Trisodium citrate	3.7
Citric acid	1.56
WFJ	1.0
Sodium hydroxide solution and/or hydrochloric acid solution	pH 5.0 ± 0.5

EXAMPLE 4. ORAL FORMULATION

Table 9 below presents a representative formulation of palonosetron formulated for oral administration.

Table 9: Representative Oral Formulation	
Ingredient	**Weight Parts (mg/ml)**
Palonosetron Hydrochloride	0.05
Mannitol	150
EDTA	0.5
Trisodium citrate	3.7
Citric acid	1.56
WFJ	1.0
Sodium hydroxide solution and/or hydrochloric acid solution	pH 5.0 ± 0.5
Flavoring	q.s.

Throughout this application, various publications are referenced. The disclosures of these publications 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.

In preferred embodiments the present invention is useful for the following methods:

1. A method of treating or preventing post-operative nausea and vomiting (PONV) in a human comprising administering from about 0.025 to about 0.075 mg of a treatment-effective amount of palonosetron or a pharmaceutically acceptable salt thereof substantially at the time of an operation.
2. The method of paragraph 1 wherein said PONV is delayed onset PONV.
3. The method of paragraph 1 wherein said administration occurs in the absence of a second administration of palonosetron or a pharmaceutically acceptable salt thereof for at least about seven days after said operation.
4. The method of paragraph 1 further comprising administering said palonosetron or a pharmaceutically acceptable salt thereof to a plurality of patients ranging in weight from about 50 to about 80 kilograms, wherein said palonosetron or pharmaceutically acceptable salt is administered in the same amount among said plurality of patients.
5. The method of paragraph 1 wherein said administration occurs from about 10 hours before to about 2 hours after said operation.

6. The method of paragraph 1 wherein about 0.025, 0.05 or 0.075 mg of palonosetron is administered intravenously.
7. The method of paragraph 1 wherein said palonsetron is administered in an intravenous formulation having a pH of about 5.
8. The method of paragraph 1 wherein said dose is administered in an intravenous formulation comprising about 0.05 mg/ml palonosetron.
9. The method of paragraph 1 wherein said dose is administered from a single unit dose vial comprising about 0.025, 0.05 or 0.075 mg of palonosetron.
10. The method of paragraph 1 wherein about 0.025, 0.05, 0.075. 0.1, 0.2, or 0.25 mg of palonosetron is administered orally.
11. The method of paragraph 1 wherein said palonosetron is administered in an oral liquid comprising about 0.05 mg/ml palonosetron.
12. The method of paragraph 1 wherein the operation is a surgery selected from a gynecologic procedure, an abdominal or gastrointestinal procedure, bowel manipulation, an ear, nose and throat or ophthalmic procedure, a hysterectomy, or a laparoscopic procedure.
13. The method of paragraph 1 wherein an anesthetic compound is administered during the operation.
14. The method of paragraph 1 wherein the palonosetron or pharmaceutically acceptable salt thereof is administered as an intravenous bolus over a time period of about 10-30 seconds.
15. The method of paragraph 1 wherein the dose of palonosetron or pharmaceutically acceptable salt thereof is from about 0.3 to about 1 microgram per kilogram of body weight of the human.
16. A method of treating or preventing delayed-onset post-operative nausea and vomiting (PONV) comprising administering a treatment effective amount of palonosetron or a pharmaceutically acceptable salt thereof substantially at the time of an operation.

17. The method of paragraph 17 wherein said administration occurs in the absence of a second administration of palonosetron or a pharmaceutically acceptable salt thereof for at least about seven days after said operation.

18. The method of paragraph 17 further comprising administering said palonosetron or a pharmaceutically acceptable salt thereof to a plurality of patients ranging in weight from about 50 to about 80 kilograms, wherein said palonosetron or pharmaceutically acceptable salt is administered in the same amount among said plurality of patients.

19. A method of rescuing a patient from the onset of post-operative nausea and vomiting (PONV) comprising administering a treatment effective amount of palonosetron or pharmaceutically acceptable salt thereof shortly after the onset of said PONV.

20. The method of paragraph 20 wherein said PONV is delayed onset PONV.

21. The method of paragraph 20 wherein said administration occurs in the absence of a second administration of palonosetron or a pharmaceutically acceptable salt thereof for at least about seven days after said operation.

22. The method of paragraph 20 further comprising administering said palonosetron or a pharmaceutically acceptable salt thereof to a plurality of patients ranging in weight from about 50 to about 80 kilograms, wherein said palonosetron or pharmaceutically acceptable salt is administered in the same amount among said plurality of patients.

23. A method of treating or preventing emesis comprising administering a single treatment effective dose of palonosetron or pharmaceutically acceptable salt thereof during a seven day period beginning substantially from an emesis inducing event.

24. The method of paragraph 24 wherein said emesis inducing event is chemotherapy or radiation therapy.

25. The method of paragraph 24 wherein said emesis inducing event is a surgery.

26. A method of treating or preventing emesis comprising administering a defined dose of palonosetron or a pharmaceutically acceptable salt thereof to a plurality of patients ranging in weight from about 50 to about 80 kilograms, wherein said defined dose is the same among said plurality of patients.
27. The method of paragraph 27 wherein said emesis inducing event is chemotherapy or radiation therapy.
28. The method of paragraph 27 wherein said emesis inducing event is chemotherapy or radiation therapy and said dose is 0.25 mg.
29. The method of paragraph 27 wherein said emesis inducing event is an operation.
30. The method of paragraph 27 wherein said emesis inducing event is an operation and said dose is 0.025, 0.05 or 0.075 mg.

CLAIMS

What is claimed is:

1. Use of from about 0.025 to about 0.075 mg of a treatment-effective amount of palonosetron or a pharmaceutically acceptable salt thereof for preparing a composition for treating or preventing post-operative nausea and vomiting (PONV) in a human the adminsistration of which being effected substantially at the time of an operation.
2. The use of claim 1 wherein said composition consists of 0.025 to about 0.075 mg of a treatment-effective amount of palonosetron or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier and/or diluent.
3. The use of one of the preceding claims wherein said administration occurs in the absence of a second administration of palonosetron or a pharmaceutically acceptable salt thereof for at least about seven days after said operation.
4. The use of one of the preceding claims wherein the composition comprises said palonosetron or a pharmaceutically acceptable salt thereof in an amount being administered in the same amount to a plurality of patients ranging in weight from about 50 to about 80 kilograms.
5. The use of one of the preceding claims wherein said administration being effected from about 10 hours before to about 2 hours after said operation.
6. The use of one of the preceding claims wherein the composition is in a form to be administered intravenously and comprises about 0.025, 0.05 or 0.075 mg of palonosetron.
7. The use of one of the preceding claims wherein the composition is an intravenous formulation comprising palonsetron and having a pH of about 5.
8. The use of one of the preceding claims wherein said dose is administered in an intravenous formulation comprising about 0.05 mg/ml palonosetron.

9. The use of one of the preceding claims wherein said composition is a single unit dose vial comprising about 0.025, 0.05 or 0.075 mg of palonosetron.
10. The use of one of the preceding claims wherein said composition is in a form to be administered orally and comprises about 0.025, 0.05, 0.075. 0.1, 0.2, or 0.25 mg of palonosetron.
11. The use of one of the preceding claims wherein said composition comprises palonosetron in an oral liquid comprising about 0.05 mg/ml palonosetron.
12. The use of one of the preceding claims wherein the administration being effected before, during or after an operation which is a surgery selected from a gynecologic procedure, an abdominal or gastrointestinal procedure, bowel manipulation, an ear, nose and throat or ophthalmic procedure, a hysterectomy, or a laparoscopic procedure.
13. The use of one of the preceding claims wherein an anesthetic compound is administered during the operation.
14. The use of one of the preceding claims for preparing an intravenous bolus comprising palonosetron or pharmaceutically acceptable salt thereof to be administered over a time period of about 10-30 seconds.
15. The use of one of the preceding claims wherein the composition comprises a dose of palonosetron or pharmaceutically acceptable salt thereof or a prodrug thereof in a range from about 0.3 to about 1 microgram per kilogram of body weight of the human in need of the treatment.
16. Use of palonosetron or a pharmaceutically acceptable salt or a prodrug thereof for preparing a composition for treating or preventing delayed-onset post-operative nausea and vomiting (PONV) the administration of an effective amount of palonosetron or a pharmaceutically acceptable salt or prodrug thereof being effected substantially at the time of an operation.
17. The use of claim 16 wherein said administration occurs in the absence of a second administration of palonosetron or a pharmaceutically acceptable salt thereof for at least about seven days after said operation.

18. The use of claim 17 further comprising administering said palonosetron or a pharmaceutically acceptable salt thereof to a plurality of patients ranging in weight from about 50 to about 80 kilograms, wherein said palonosetron or pharmaceutically acceptable salt is administered in the same amount among said plurality of patients.
19. Use of a treatment effective amount of palonosetron or pharmaceutically acceptable salt thereof for preparing a composition for rescuing a patient from the onset of post-operative nausea and vomiting (PONV) the administration of a treatment effective amount of palonosetron or pharmaceutically acceptable salt thereof being shortly after the onset of said PONV.
20. The use of one of the preceding claims wherein said PONV is delayed onset PONV.
21. The use of one of the preceding claims wherein the composition comprises a defined dose of palonosetron or a pharmaceutically acceptable salt therof in an amount useful for a plurality of patients ranging in weight from about 50 to about 80 kg and a pharmaceutically acceptable carrier and/or diluent.
22. Use of a single treatment effective dose of palonosetron or pharmaceutically acceptable salt thereof for preparing a medicament for treating or preventing emesis during a seven day period beginning substantially from an emesis inducing event.
23. The use of claim 22 wherein said emesis inducing event is chemotherapy or radiation therapy.
24. The use of claim 22 wherein said emesis inducing event is a surgery.
25. The use of claim 22 wherein said emesis inducing event is an operation and said dose is 0.025, 0.05 or 0.075 mg.
26. The use of one of the preceding claims wherein a prodrug of palonosetron is used.
27. Composition for treating or preventing post-operative nausea and vomiting (PONV) in a human the administration of which being effected substantially at

the time of an operation consisting of 0.025 to about 0.075 mg of a treatment-effective amount of palonosetron or a pharmaceutically acceptable salt or prodrug thereof and a pharmaceutically acceptable carrier and/or diluent.

28. Intravenous formulation for treating or preventing post-operative nausea and vomiting (PONV) in a human comprising 0.025 to 0.075 mg palonosetron or a pharmaceutically acceptable salt or prodrug thereof and a pharmaceutically acceptable carrier and/or diluent and having a pH of about 5.

29. Intravenous bolus for treating or preventing post-operative nausea and vomiting (PONV) in a human comprising a dose of palonosetron or pharmaceutically acceptable salt thereof or a prodrug thereof in a range from about 0.3 to about 1 microgram per kilogram of body weight of the human in need of the treatment.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

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Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, WPI Data, EMBASE, MEDLINE, SCISEARCH, BIOSIS, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	TANG, JUN ET AL: "The efficacy of RS-25259, a long-acting selective 5-HT3 receptor antagonist, for preventing postoperative nausea and vomiting after hysterectomy procedures" ANESTHESIA & ANALGESIA (BALTIMORE) (1998), 87(2), 462-467 , XP009027884	1-26
A	page 462, column 1, paragraph 1 page 462, column 2, paragraph 3 page 464, column 2, paragraph 3 -page 466, column 2, paragraph 2	27-29

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP2004/001558

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(71) Applicant *(for all designated States except US)*: **HELSINN HEALTHCARE SA** [CH/CH]; P.O. Box 357, CH-6915 Pambio-Noranco, Lugano (CH).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **MACCIOCCHI, Alberto** [CH/CH]; Pizzo Ferraro, CH-6807 Taverne (CH). **CANTOREGGI, Sergio** [CH/CH]; Via Ai Ronchi, 37, CH-6934 Vezia (CH). **BRAGLIA, Enrico** [CH/CH]; Via Pian Scairolo 9, CH-6912 Pazzallo (CH). **BRAGLIA, Riccardo** [CH/CH]; Via Pian Scairolo 9, CH-6912 Pazzallo (CH).

(74) Agent: **LEISSLER-GERSTL, Gabriele**; Eisenführ, Speiser & Partner, Arnulfstr. 25, 80335 München (DE).

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(54) **Title:** PALONOSETRON FOR THE TREATMENT OF CHEMOTHERAPY-INDUCED EMESIS

(57) **Abstract:** Methods and compositions for reducing chemotherapy and radiotherapy induced emesis with 5-HT_3 receptor antagonists are disclosed, especially with palonosetron.

WO 2004/045615 A1

PALONOSETRON FOR THE TREATMENT OF CHEMOTHERAPY-INDUCED EMESIS

FIELD OF THE INVENTION

The present invention relates to methods for reducing chemotherapy and radiotherapy induced emesis with 5-HT_3 receptor antagonists. In particular, the invention relates to methods for reducing chemotherapy and radiotherapy induced emesis with palonosetron.

BACKGROUND OF THE INVENTION

Emesis is a devastating consequence of cytotoxic chemotherapy and radiotherapy that drastically affects the quality of life of people undergoing such treatment. In recent years a class of drugs referred to as 5-HT_3 (5-hydroxytryptamine) receptor antagonists has been developed that treat such emesis by antagonizing cerebral functions associated with the 5-HT_3 receptor. See *Drugs Acting on 5-Hydroxytryptamine Receptors*: The Lancet Sep. 23, 1989 and refs. cited therein. Drugs within this class include ondansetron, granisetron and dolasetron, as disclosed in U.S. Pat. Nos. 4,695,578, 4,753,789, 4,929,632, 5,240,954, 5,578,628, 5,578,632, 5,922,749, 5,622,720, 5,955,488, and 6,063,802 (ondansetron), 4,906,755, 5,011,846, and 4,906,755 (dolasetron), and 4,886,808, 4,937,247, 5,034,398 and 6,294,548 (granisetron).

These 5-HT_3 antagonists are typically administered intravenously shortly before chemotherapy or radiotherapy is initiated, and can be administered more than once during a cycle of chemotherapy or radiotherapy. For example, when a chemotherapeutic agent is administered more than once in a cycle (as for example on days 1-7 in a 28 day chemotherapy cycle), the 5-HT_3 antagonist can be administered on each of days 1-7 for optimum anti-emetogenic effect. Because some chemotherapeutic agents can induce emesis over extended periods of several days even when they are administered only once, it would be desirable to administer an emesis-inhibiting drug such as a 5-HT_3 antagonist

every day until the risk of emesis has substantially subsided. The present class of 5-HT_3 antagonists has not proven especially helpful meeting this need, however, because the 5-HT_3 receptor antagonists currently marketed have proven to be less effective in controlling delayed nausea and vomiting than they are at controlling acute emesis. Sabra, K, *Choice of a 5HT$_3$ Receptor Antagonist for the Hospital Formulary.* EHP, Oct. 1996;2 (suppl 1):S19-24.

Each of the currently available 5-HT_3 antagonists also suffers from one or more of the following deficiencies which limits its therapeutic utility: potency, duration of effect, window of therapeutic efficacy, ease of dosing, side effects, and certainty of the dosing regimen. Sabra, K (1996) (supra). Although side effects are typically mild to moderate and transient, they include headache, lightheadedness or dizziness, abdominal pain or cramping, constipation, sedation and fatigue, elevations in hepatic transaminases and/or bilirubin, and electrocardiographic changes. Gregory , RE and Ettinger, DS, *5HT$_3$ receptor antagonists for the prevention of chemotherapy-induced nausea and vomiting. A comparison of their pharmacology and clinical efficacy.* Drugs, Feb 1998;55(2):173-189.

Various patents and references disclose classes of compounds useful as emesis-inhibiting agents and 5-HT_3 antagonists. For example, Ponchant et al., "Synthesis of 5-^{125}I-Iodo-Zacopride, A New Probe for 5-HT_3 Receptor Sites," J. Lab. Cpds. and Radiopharm., Vol. XXIX, No. 10, pp. 1147-1155 (1991) discloses substituted 3-quinuclidinyl benzamides useful for 5-HT_3 serotonin receptor binding. U.S. Pat. No. 4,717,563 to Alphin et al., discloses a method of controlling emesis caused by non-platinum anti-cancer drugs utilizing particular N-3-quinuclidinyl benzamides and thiobenzamides. U.S. Pat. No. 4,820,715 to Monkovic et al. discloses substituted 3-quinuclidinyl benzamide compounds which are asserted to be useful for the treatment of emesis, such as chemotherapy-induced emesis, and/or treatment of disorders related to impaired gastric motility. U.S. Patent No. 5,202,303 to Berger et al. discloses a class of benz[*de*]isoquinolin-1-ones that act as 5-HT_3 receptor antagonists. Species disclosed in the patent include palonosetron. According to this patent, the class of compounds is useful to treat emesis, gastrointestinal disorders, anxiety, depressive states, and pain. The patent does not disclose any particular data for determining a suitable therapeutic regimen

such as the potency of the compounds, the serum half life of the compounds, dose response data, or duration of effect.

One of the greatest challenges in drug dosing, especially when multiple doses are administered over a period of a few days, is to find a dose that is well-tolerated and consistently efficacious throughout the dosing regimen. Finding an optimum dose is complicated by such factors as serum half-life, dosing/efficacy relationships, and, in the case of anti-emetic drugs, the variability of the chemotherapeutic regimen with which the drugs will be administered and the types of emesis induced (i.e. delayed v. acute emesis and moderately v. highly emetogenic chemotherapy). This challenge is particularly acute when devising single unit dose formulations of the anti-emetic drug that is efficacious over a range of body weights, because single unit dose forms are designed typically to prevent nurses and doctors from titrating the dose in the clinic.

OBJECTS OF THE INVENTION

It is an object of the present invention to provide methods of inhibiting emesis using 5-HT_3 receptor antagonists that have heightened potency, and that can be administered in lower doses to yield fewer incidences of unwanted side effects.

It is another object of the invention to provide methods of inhibiting and relieving acute and delayed emesis induced by chemotherapeutic agents or radiotherapy, and drugs having the capacity to inhibit and relieve such acute and delayed emesis.

Another object of the present invention is to provide a uniform defined dose of palonosetron that can be administered to a patient of nearly any body weight in successive 24 hour periods to control immediate and delayed emesis.

Still another object of the present invention is to provide 5-HT_3 antagonists that possess increased plasma half-life and prolonged *in vivo* activity.

Another object of the invention is to provide greater flexibility when administering emesis-inhibiting agents in advance of chemotherapeutic regimens or radiotherapy, by increasing the size of the window for pretreatment.

Yet another object of the invention is to provide greater flexibility when administering an emesis-inhibiting agent, by reducing the time required to administer a bolus of the emesis-inhibiting agent

Still another object of the present invention is to provide more definite regimens for the treatment of chemotherapeutically or radiotherapeutically induced emesis, by preventing doctors from prescribing unnecessarily increased dosages of palonosetron, and allowing doctors to switch to other anti-emetic agents when palonosetron does not prove effective rather than increasing the dose.

SUMMARY OF INVENTION

Contrary to published reports that 5-HT_3 antagonists have minimal benefit in the treatment or prevention of delayed emesis, the inventors have surprisingly discovered that palonosetron alleviates and prevents acute and delayed emesis in both moderately and highly emetogenic chemotherapy regimens, and that palonosetron is substantially superior to both ondansetron and dolasetron in its ability to prevent and alleviate nausea and vomiting that occurs more than 24 hours after the initiation of moderately emetogenic chemotherapy. Therefore, in one embodiment the invention provides a method of treating acute and delayed emesis in a patient undergoing emetogenic chemotherapy or radiotherapy comprising administering a treatment effective amount of palonosetron. The treatment effective amount is preferably one of the doses disclosed in greater detail elsewhere in this document.

The inventors have also made a series of discoveries that support a surprisingly effective and versatile clinical regimen for the treatment and prevention of emesis using palonosetron. In particular, the inventors have discovered:

- that palonosetron can treat and prevent emesis induced by chemotherapy and radiotherapy at levels of only about $1/10^{th}$ the levels of other 5-HT_3 antagonists;
- that palonosetron has a plasma half-life of about 40 hours; and
- that the efficacy of palonosetron plateaus over a broad range of doses ranging from about 30 *u*g/kg to about 90 *u*g/kg.

Based upon the foregoing discoveries, the inventors have determined that 0.25 mg/day of palonosetron is a particularly effective and versatile dose of palonosetron for use in the clinic because the dose is effective when used only once in a chemotherapy or radiotherapy cycle, but it is also effective when administered on successive days because, in spite of the long half-life of palonosetron and a concomitant build-up of palonosetron

during the multiple doses, consistent efficacy can be expected from each dose of palonosetron due to the observed plateau effect. Moreover, such efficacy can be expected over a wide range of patient body weights.

Therefore in another embodiment the invention provides a method of treating chemotherapy or radiotherapy-induced emesis in a patient comprising administering a dose of 0.25 mg of palonosetron to the patient. In another embodiment the invention provides single unit dosage forms of palonosetron that comprise 0.25 mg of palonosetron.

The surprising potency of palonosetron, the extended plasma half-life of palonosetron, and the plateau dosing phenomena observed for palonosetron, also have a number of other practical advantages including:

- The potency of palonosetron allows for greater cost efficiencies because lesser quantities of palonosetron are needed.
- The potency of palonosetron also allows the manufacturer to formulate the drug at reduced concentrations. This advantage is of particular significance in the formulation of palonosetron because palonosetron has been found to be most stable at lower concentrations. This advantage is also significant from a convenience standpoint because the palonosetron can be sufficiently concentrated to be intravenously administered as a bolus in only about from 10 to 30 seconds.
- The extended plasma half-life reduces even further the quantity of palonosetron that must be administered to treat emesis.
- The extended half-life allows the palonosetron to be administered at intervals of about 24 hours, or only once in certain therapeutic settings.
- The extended half-life allows greater flexibility in a clinical setting by allowing the drug to be administered over a larger window of time preceding the administration of chemotherapy or radiotherapy.
- The extended half-life and plateau dosing phenomena combine to provide more certainty to the regimen by assuring the physician that a further dose of palonosetron in a session is not warranted within a particular window of time even if emesis is experienced.

- The extended half-life and plateau dosing phenomena further combine to provide more certainty to the regimen by avoiding the tendency of physicians to increase the dose of palonosetron in subsequent sessions if emesis is experienced in a prior session.

DEFINITIONS

"Ampule" means a small sealed container of medication that is used one time only, and includes breakable and non-breakable glass ampules, breakable plastic ampules, miniature screw-top jars, and any other type of container of a size capable of holding only one unit dose of palonosetron (typically about 5 mls.).

"Animal" includes humans, non-human mammals (e.g., dogs, cats, rabbits, cattle, horses, sheep, goats, swine, and deer) and non-mammals (e.g., birds and the like). While the methods disclosed herein are generally applicable to people, they are applicable as well to animals.

"Chemotherapeutic agents" include a variety of classes of compounds for treating proliferative disorders including alkylating agents, antimetabolites, natural products, enzymes, biological response modifiers, miscellaneous agents, radiopharmaceuticals (for example, Y-90 tagged to hormones or antibodies), hormones and antagonists, such as those listed below.

Antiangiogenesis Agents: Angiostatin, Endostatin.

Alkylating Agents: Nitrogen Mustards such as Mechlorethamine, Cyclophosphamide, Ifosfamide, Melphalan (L-sarcolysin),and Chlorambucil; Ethylenimines and Methylmelamines such as Hexamethylmelamine and Thiotepa; Alkyl Sulfonates such as Busulfan; Nitrosoureas such as Carmustine (BCNU), Lomustine (CCNU), Semustine (methyl-CCNU), and Streptozocin (STR); and Triazenes such as Dacarbazine (DTIC; dimethyltriazenoimidazole-carboxamide).

Antimetabolites: Folic Acid Analogs such as Methotrexate (amethopterin); Pyrimidine Analogs such as Fluorouracil (5-fluorouracil; 5-FU), Floxuridine (fluorodeoxyuridine; FUdR), and Cytarabine (cytosine arabinoside); Purine Analogs and Related Inhibitors such as Mercaptopurine (6-mercaptopurine; 6-MP), Thioguanine (6-thioguanine: TG), and Pentostatin (2'-deoxycyoformycin); Vinca Alkaloids such as

Vinblastine (VLB), and Vincristine; and Epipodophylotoxins such as Etoposide and Teniposide.

Natural Products: Antibiotics such as Dactinomycin (actinonmycin D), Daunorubicin (daunomycin; rubidomycin), Doxorubicin, Bleomycin, Plicamycin (mithramycin), and Mitomycin (mitomycin C); Enzymes such as L-Asparaginase; and Biological Response Modifiers such as Interferon-alfa.

Miscellaneous Agents: Platinum Coordination Complexes such as Cisplatin (cis-DDP) and Carboplatin; Mixtozantrone; Hydroxyurea; Procarbazine (N-methylhydrazine, MIH); Mitotane (o,p'-DDD); Aminoglutethimide; Adrenorticosteriods such as Prednisone; and Progestins such as Hydroxprogesterone caproate, Medroxyprogesterone acetate, and Megestrol acetate.

Hormones and Antagonists: Estrogens such as Diethylstibestrol and Ethinyl estradiol; Antiestrogens such as Tamoxifen; Androgens such as Testosterone propionate Fluxomyesterone; Antiandrogens such as Flutamide (prostate); and Gonadotropin-Releasing Hormone Analog such as Leuprolide.

Throughout this specification the word "comprise," or variations such as "comprises" or "comprising," will be understood to imply the inclusion of a stated element, integer or step, or group of elements, integers or steps, but not the exclusion of any other element, integer or step, or group of elements, integers or steps

"Disease" specifically includes any unhealthy condition of an animal or part thereof and includes an unhealthy condition which may be caused by, or incident to, medical or veterinary therapy applied to that animal, i.e., the side effects of such therapy. Thus, disease here includes the emesis caused by therapy with agents having emetogenic side effects, in particular by therapy for cancer, such as chemotherapy with chemotherapeutic agents and radiotherapy.

"Emesis", for the purposes of this application, will have a meaning that is broader than the normal, dictionary definition and includes not only vomiting, but also nausea and retching.

"Delayed emesis" means emesis that occurs greater than about 24 hours after initiation of an emesis inducing chemotherapeutic or radiotherapeutic event. Delayed

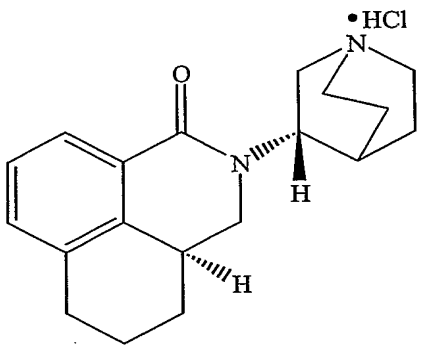
emesis thus includes emesis that occurs up to 2, 3, 4, or even 5 days after a chemotherapeutic or radiotherapeutic event.

"Acute emesis" refers to emesis that involves vomiting within 24 hours of initiation of an emesis inducing chemotherapeutic or radiotherapeutic event.

"Moderately emetogenic chemotherapy" refers to chemotherapy in which the emetogenic potential is comparable or equivalent to the emetogenic potential of carboplatin, cisplatin ≤ 50 mg/m^2, cyclophosphamide < 1500 mg/m^2, doxorubicin > 25 mg/ms, epirubicin, irinotecan, or methotrexate > 250 mg/m^2.

"Highly emetogenic chemotherapy" refers to chemotherapy in which the emetogenic potential is comparable or equivalent to the emetogenic potential of cisplatin ≥ 60 mg/m^2, cyclophosphamide > 1500 mg/m^2, or dacarbazine.

"Palonosetron" means (3aS)-2,3,3a,4,5,6-Hexahydro-2-[(S)-1-Azabicyclo[2.2.2]oct-3-yl]2,3,3a,4,5,6-hexahydro-1-oxo-1*H*benz[*de*]isoquinoline hydrochloride, and is preferably present as the monohydrochloride. Palonosetron monohydrochloride can be represented by the following chemical structure:



"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.

"Pharmaceutically acceptable salts" means salts which are pharmaceutically acceptable, as defined above, and which possess the desired pharmacological activity. Such salts include acid addition salts formed with inorganic acids such as hydrochloric

acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or with organic acids such as acetic acid, propionic acid, hexanoic acid, heptanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, o-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2,-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid p-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, p-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like.

In addition, pharmaceutically acceptable salts may be formed when an acidic proton present is capable of reacting with inorganic or organic bases. Acceptable inorganic bases include sodium hydroxide, sodium carbonate, potassium hydroxide, aluminum hydroxide and calcium hydroxide. Acceptable organic bases include ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine and the like.

"Therapeutically effective amount" means that amount which, when administered to an animal for treating a disease, is sufficient to effect such treatment for the disease.

"Treating" or "treatment" of a disease includes: (1) preventing the disease from occurring in an animal which may be predisposed to the disease but does not yet experience or display symptoms of the disease, (2) treating the disease, i.e., arresting its development, or (3) relieving the disease, i.e., causing regression of the disease.

DETAILED DISCUSSION

One embodiment of the present invention is premised upon the discovery that palonosetron is surprisingly superior to other 5-HT_3 antagonists in its ability to treat delayed emesis, while exhibiting remarkable efficiency at treating acute emesis as well. Thus, in one embodiment, the invention provides a method of treating chemotherapy or radiotherapy induced delayed and acute emesis comprising administering a treatment-

effective amount of palonosetron. The method is effective for the treatment of emesis induced by both moderately emetogenic chemotherapy and highly emetogenic chemotherapy.

In another embodiment the invention provides a method for treating acute and/or delayed emesis comprising (a) administering to a human or other animal from about 1 to about 10 *u*g/kg of palonosetron, and (b) administering to said human or other animal an emesis inducing amount of a chemotherapeutic agent or radiotherapy. While larger doses of palonosetron of up to about 30, 60, or 90 *u*g/kg, can be administered effectively to reduce emesis, it has surprisingly been found that the effectiveness of palonosetron typically plateaus at these lower concentrations in the chemotherapeutic regimens tested. Therefore, in a preferred embodiment, from about 3 to about 10 *u*g/kg of palonosetron is administered. In another embodiment the palonosetron is administered in the absence of a steroid such as dexamethasone.

In another embodiment the invention provides a method of treating chemotherapy or radiotherapy-induced emesis in a patient comprising administering a dose of 0.25 mg of palonosetron to the patient. This dose has been found to be effective over a range of body weights from about 40 to about 120 kilograms , and can conveniently be provided in single unit dose ampules that need not be titrated based upon a patient's body weight within this range. The dose is effective to treat chemotherapy-induced delayed and acute emesis. In addition, the dose is effective for the treatment of emesis induced by both moderately emetogenic chemotherapy and highly emetogenic chemotherapy.

A particularly surprising advantage of the lower dosages required of palonosetron derives from the fact that the stability of palonosetron increases in solution as its concentration decreases. The potency of palonosetron thus allows the palonosetron to be formulated in stable compositions comprising a wide range of palonosetron concentrations, preferably from about 0.01 mg/ml to about 0.20 mg/ml palonosetron, most preferably at a concentration of about 0.05 mg/ml. Thus, in one particular embodiment the palonosetron is supplied in ampules that comprise 5 ml. of solution, which equates to about 0.25 mg of palonosetron at a concentration of about 0.05 mg/ml.

The enhanced stability allows the palonosetron to be stored for extended periods of time, exceeding about 1 month, 3 months, 6 months, 1 year, or 18 months, but preferably not extending beyond 30 months (we are testing the stability, which shall be included in the FDA file). This enhanced stability is seen in a variety of storage conditions, including room temperature.

The method can be practiced using virtually any method of administration including oral, systemic (e.g., transdermal, intranasal or by suppository) or parenteral (e.g., intramuscular, intravenous or subcutaneous). In a preferred embodiment the palonosetron is administered as an oral liquid or intravenously, and most preferably the palonosetron is administered intravenously.

Another particular advantage associated with the lower dosages of palonosetron is the ability to administer the drug in a single intravenous bolus over a short, discrete time period. This time period generally extends from about 10 to about 60 seconds, or about 10 to about 40 seconds, and most preferably is about 10 to 30 seconds.

Still other embodiments pertain to the sequence and timing of steps in which the method is performed. Although the method can be performed in any sequence, in a preferred embodiment step (a) (the palonosetron administration) precedes step (b) (the chemotherapy or radiotherapy administration) in sequence. Moreover, while step (a) can be performed over a large window of time preceding step (b), from immediately before step (b) to as long as 1, 2, 5, 8, or 10 hours before step (b), the palonosetron is preferably administered from about 15 minutes to about 2 hours before the chemotherapeutic agent or radiotherapy, more preferably from about 15 minutes to about 1 hour before the chemotherapeutic agent or radiotherapy, and most preferably about 30 minutes before the chemotherapy agent or radiotherapy.

The methods of the present invention are preferably performed in the context of chemotherapeutic or radiotherapy cycles, in which an intensive regimen of chemotherapy or radiotherapy is administered over a defined time period, followed by an extended recovery period, and a subsequent cycle in which the therapy and recovery sequence is repeated. An intensive regimen of chemotherapy may comprise only one administration of a chemotherapeutic agent, or it may comprise several days of administering the same

chemotherapeutic agent. Similarly, the regimen may include the administration of more than one chemotherapeutic agents. Moreover, one or more of the chemotherapeutic agents may induce acute and/or delayed emesis.

Palonosetron is preferably administered in conjunction with the chemotherapy or radiotherapy based upon when emesis is most likely to be experienced, at time intervals of about 24 hours. For example, if an emesis inducing chemotherapeutic agent that induces acute emesis and not delayed emesis is administered only once during a cycle of chemotherapy (i.e. in one session), palonosetron will be administered only once as well. If the chemotherapeutic agent induces acute and delayed emesis, then palonosetron will preferably be administered at the initiation of the chemotherapy and every 24 hours thereafter until the emesis has subsided. Similarly, if an emesis inducing agent is administered more than once during a chemotherapy cycle (i.e. in more than one session), then palonosetron will preferably also be administered more than once every 24 hours.

The methods of the present invention are useful for treating emesis induced by a wide range of chemotherapeutic agents and radiotherapies discussed above, but are particularly useful when employed in conjunction with cisplatin, cyclophosphamide, carmustine, dicarbazine, actinomycin D, mechlorethamine, carboplatin, doxorubicin, epirubicin, irinotecan, methotrexate, and dacarbazine. The methods have also been found to be particularly useful when used in conjunction with highly emetogenic chemotherapy, especially when using chemotherapeutic agents that are typically associated with extended periods of emesis, or delayed onset of emesis. In various embodiments, the chemotherapeutic agent induces emesis for a period of at least about 24 hours, 48 hours, 72 hours, or 5 days. For example, in one embodiment the chemotherapeutic agent is cisplatin or cyclophosphamide, and in still further preferred embodiments the cisplatin is administered at a dose exceeding about 30, 40, 50, 60, or 70 mg/m^2, and the cyclophosphamide is administered at a dose exceeding about 500, 600, 700, 800, 900, 1000, or 1100 mg/m^2.

The plateau effects observed with increasing doses of palonosetron, combined with its extended half-life, further combine to inform the prescribing physician of appropriate regimens to be followed when a patient is at least partially non-responsive to palonosetron. For example, under some circumstances the physician will be assured that

he should switch the patient from palonosetron in a subsequent session rather than administer a higher dose of palonosetron. Therefore, in another embodiment the invention provides a method of preventing chemotherapy induced emesis comprising: (1) in a first chemotherapeutic session: administering to a human or other animal a first amount of palonosetron; and administering to said human or other animal an emesis inducing amount of a chemotherapeutic agent; (2) assessing the effectiveness of the palonosetron; and (3) in a subsequent chemotherapeutic session, if said human or other animal is at least partly non-responsive to said palonosetron in said first chemotherapeutic session, administering to said human or other animal a therapeutically effective amount of a second anti-emetic compound; wherein the subsequent chemotherapeutic session is performed without an intervening chemotherapeutic session in which a second amount of palonosetron higher than the first amount is administered.

The plateau dosing effect, when combined with the extended serum half life, can also render the dosing regimen in some circumstances more certain by avoiding the tendency of physicians to prematurely administer additional doses of palonosetron in a single therapeutic session if emesis is experienced. Thus, in another embodiment the invention provides a method of preventing chemotherapy induced emesis comprising, (1) in one chemotherapeutic session: administering to a human or other animal a first dose of palonosetron; and administering to said human or other animal an emesis inducing amount of a chemotherapeutic agent; (2) assessing the effectiveness of the palonosetron; and (3) if said human or other animal is at least partly non-responsive to said first dose of palonosetron, not administering a second dose of palonosetron for at least about 20, 24, 28, or 32 hours after step (a) or (b).

PHARMACEUTICAL COMPOSITIONS

Although the foregoing discussion has focused upon intravenous administration of palonosetron because that is the preferred mode of administration, the methods of the present invention can be performed by administering palonosetron by any one of the following routes: oral, systemic (e.g., transdermal, intranasal or by suppository) or parenteral (e.g., intramuscular, intravenous or subcutaneous).

Oral compositions will generally include an inert diluent or an edible carrier. They may be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, 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.

The 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; a glidant 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 compound can be administered as a component of an elixir, suspension, syrup, wafer, 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.

The compound or a pharmaceutically acceptable prodrug or salts thereof can also be mixed with other active materials that do not impair the desired action, or with materials that supplement the desired action, such as antibiotics, antifungals, anti-inflammatories, or other antivirals, including other nucleoside compounds. Solutions or suspensions used for parenteral, intradermal, subcutaneous, or topical application 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 or dextrose. The parental

preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

If administered intravenously, preferred carriers are physiological saline or phosphate buffered saline (PBS).

Preferably the pharmaceutical composition is administered in a single unit dosage form for continuous treatment or in a single unit dosage form ad libitum when relief of symptoms is specifically required.

EXAMPLES

Example 1: Antiemetic Effects of Palonosetron in Animal Models

The antiemetic effects of intravenously and orally administered palonosetron were assessed in male and female dogs (sexes combined). Antineoplastic agents employed in these experiments included cisplatin (3 mg/kg)), dacarbazine (30 mg/kg) , mechlorethamine (0.4 mg/kg) and actinomycin D (0.15 mg/kg).

Palonosetron and comparator drugs were administered prior to or after antineoplastic agents and animals were observed for the number of emetic episodes. Mean numbers of episodes were computed and the statistical significance of differences between treatment groups were determined with Dunnett's t test. Solutions of palonosetron and comparator drugs (ondansetron and granisetron) were prepared in distilled water. Vehicle control groups received distilled water.

The therapeutic effects of intravenously and orally administered palonosetron were compared to those of ondansetron and vehicle in cisplatin-treated dogs. When administered by the intravenous route, both palonosetron (0.1 mg/kg) and ondansetron (1.0 mg/kg) reduced the number of emetic episodes during the five-hour period following administration of cisplatin 3.0 mg/kg. Palonosetron was statistically significantly more potent than ondansetron based on the mean number of emetic episodes observed (2.20 and 6.83 for palonosetron and ondansetron, respectively, compared with 12.50 for vehicle control).

In a different study, palonosetron and ondansetron were assessed for their relative abilities to reverse cisplatin-induced emesis. In these experiments dogs received

intravenous injections of palonosetron, ondansetron, or vehicle one hour after the intravenous administration of 3.0 mg/kg cisplatin. Each animal was observed continuously for five hours following cisplatin administration for the number of emetic episodes. The results of this experiment are summarized in Table 1.

Table 1. Therapeutic Effect of Intravenously Administered Palonosetron and Ondansetron on Cisplatin-Induced Emesis in Dogs

Treatment	N	Intravenous Dose (μg/kg)	Emetic Episodes (mean ± SD)
Vehicle control	6	0.0	13.50 ± 5.89
Palonosetron	6	0.3	13.16 ± 6.11
	6	1.0	7.16 ± 4.26[a]
	6	3.0	4.33 ± 4.03[b]
	6	10.0	4.50 ± 5.24[b]
	6	30.0	1.33 ± 1.21[b]
	6	100.0	1.67 ± 1.83[b]
	6	300.0	3.33 ± 3.01[b]
Ondansetron	6	1.0	16.16 ± 5.14
	6	3.0	13.33 ± 4.17
	6	10.0	13.33 ± 3.01
	6	30.0	8.33 ± 3.20
	6	100.0	4.83 ± 2.40[b]
	6	300.0	1.00 ± 2.00[b]
	6	1000.0	1.16 ± 0.40[b]

[a] Significantly less than vehicle control, $p < 0.05$.
[b] Significantly less than vehicle control, $p < 0.01$.

The statistically minimally effective dose level was 1.0 μg/kg for palonosetron and 100 μg/kg for ondansetron, suggesting that palonosetron was substantially more potent than ondansetron in this experiment.

The observation of potency differential was further seen during an experiment in which oral dose-response relationships of palonosetron and ondansetron were compared in cisplatin-treated dogs. Palonosetron, ondansetron or vehicle control were administered by the oral route one hour prior to the administration of cisplatin. Each animal was

observed continuously for five hours following cisplatin administration for the number of emetic episodes. The results of this experiment are summarized in Table 2.

Table 2. Anti-Emetic Effect in Male and Female Dogs of Palonosetron or Ondansetron Orally Administered One Hour Before Cisplatin

Treatment	N	Oral Dose (μg/kg)	Emetic Episodes (mean ± SD)
Vehicle control	6	0.0	14.16 ± 7.98
Palonosetron	6	0.3	12.16 ± 1.94
	6	1.0	12.83 ± 4.70
	6	3.0	16.16± 5.11
	6	10.0	4.00 ± 3.79[a]
	6	30.0	2.66 ± 1.75[a]
	6	100.0	0.00 ± 0.00[a]
	6	300.0	1.67 ± 2.04 [a]
Ondansetron	6	1.0	15.50 ± 3.93
	6	3.0	14.83 ± 6.49
	6	10.0	12.66 ± 3.01
	6	30.0	18.33 ± 8.43
	6	100.0	10.50 ± 3.14
	6	300.0	3.16 ± 1.32[a]
	6	1000.0	2.00 ± 2.09[a]

a Significantly less than vehicle control, $p < 0.01$.

Pretreatment with both palonosetron and ondansetron reduced the incidences of emetic episodes. Palonosetron exhibited the greater potency as evidenced by a significant reduction in episodes after 10 μg/kg as compared to the minimally effective dose of 300 μg/kg for ondansetron.

Example 2: Duration of Action in Cisplatin-Treated Dogs

The durations of action of intravenously administered palonosetron, ondansetron and granisetron in dogs were compared in an experiment, the results of which are shown in Table 3. In this study groups of six dogs received intravenous doses of palonosetron, ondansetron, or granisetron (0.1, 0.15, or 0.04 mg/kg, respectively), or vehicle control 12, 10, 8, 6, 4, 2, or 1 hour prior to the intravenous injection of 3.0 mg/kg of cisplatin.

Table 3. Duration of Action of Intravenously Administered Palonosetron, Ondansetron, or Granisetron in Cisplatin-Dosed Dogs

Pre-Cisplatin (hr)	Treatment	Dose (mg/kg)	Emetic Episodes (mean ± SD)
12	Vehicle	0	17.33 ± 4.68
	Palonosetron	0.1	13.17 ± 6.27
	Ondansetron	0.15	22.00 ± 8.32
	Granisetron	0.04	15.67 ± 6.28
10	Vehicle	0	19.33 ± 5.68
	Palonosetron	0.1	9.83 ± 4.79[b]
	Ondansetron	0.15	13.83 ± 4.58
	Granisetron	0.04	23.00 ± 5.87
8	Vehicle	0	20.00 ± 4.94
	Palonosetron	0.1	9.50 ± 5.50[b]
	Ondansetron	0.15	15.50 ± 7.29
	Granisetron	0.04	14.67 ± 8.69
6	Vehicle	0	17.33 ± 7.66
	Palonosetron	0.1	5.83 ± 4.40[b]
	Ondansetron	0.15	14.17 ± 6.79
	Granisetron	0.04	21.33 ± 9.54
4	Vehicle	0	12.67 ± 2.34
	Palonosetron	0.1	0.33 ± 0.52[b]
	Ondansetron	0.15	12.67 ± 2.07
	Granisetron	0.04	13.83 ± 7.25
2	Vehicle	0	12.00 ± 6.20
	Palonosetron	0.1	2.50 ± 2.43[b]
	Ondansetron	0.15	10.67 ± 5.28
	Granisetron	0.04	9.67 ± 4.46
1	Vehicle	0	13.83 ± 4.36
	Palonosetron	0.1	1.33 -+ 1.03[b]
	Ondansetron	0.15	7.83 ± 4.12[b]
	Granisetron	0.04	12.33 ± 4.32

a For each treatment group, n = 6 and the vehicle control was distilled water.
b Significantly less than vehicle control, $p < 0.05$ using Fisher's LSD strategy.

Palonosetron exhibited some antiemetic activity when administered as long as 10 hours before the injection of cisplatin. Ondansetron reduced emetic episodes only after a one-hour pretreatment period. Granisetron was without antiemetic effect in these experiments. Palonosetron did not protect when administered 12 hours before cisplatin. In an earlier experiment, a higher dose of ondansetron (0.3 mg/kg, IV) exhibited protective effects when administered as long as seven hours prior to injection of cisplatin. In that experiment, a dose of 0.03 mg/kg of palonosetron was similarly effective. The results of these experiments support the conclusion that the duration of antiemetic action of palonosetron is longer than that of ondansetron, and that a higher dose of ondansetron is required to achieve an equivalent effect.

Example 3: Relationship Between Systemic Exposure and Antiemetic Effect

An experiment was conducted to study the relationship between plasma concentration of palonosetron and protection of dogs against cisplatin-induced emesis. Groups of dogs received oral doses of palonosetron (0, 100, 316, or 1000 µg/kg) or vehicle control 30 minutes prior to the injection of cisplatin. Plasma concentrations of palonosetron were determined by an HPLC-radioimmunoassay method at 0, 0.25, 0.5, 1, 2, 4, 8, 24, and 48 hours after administration of palonosetron and systemic exposure was expressed as AUC0-4 hr. Results are summarized in Table 4.

Table 4. Systemic Exposure of Palonosetron ($AUC_{0\text{-}4hr}$) in Dogs After Intravenous Administration and Effects on Cisplatin-Induced Emesis

Palonosetron (µg/kg)	N	$AUC_{0\text{-}4hr}$ (mean ± SD)	Emetic Episodes (mean ± SD
0 (vehicle)	6	0.00 ± 0.00[a]	15.83 ± 3.43
100	6	10.59 ± 7.24[a]	1.83 ± 1.60[b]
316	6	30.64 ± 12.02[a]	4.50 ± 6.83[b]
1000	6	76.07 ± 50.39[a]	5.67 ± 5.32[b]

[a] Significantly different from all other AUCs, $p < 0.01$.
[b] Significantly different from controls, $p < 0.05$.

Systemic exposure to palonosetron, as estimated by computed AUC_{0-4hr} values, were approximately dose-proportional over the range studied, however, a relationship between systemic exposure and magnitude of antiemetic effect could not be demonstrated. Dogs dosed with palonosetron had significantly fewer emetic episodes than vehicle control animals but there was no evidence of a significant dose-response relationship. The lowest dose tested appeared to be at the response plateau.

Example 4: Antagonism of Emetic Effects of Dacarbazine, Actinomycin D, and Mechlorethamine

The protective effects of palonosetron and ondansetron against emesis caused by the administration of dacarbazine, actinomycin D, or mechlorethamine were assessed in dogs. In these experiments palonosetron, ondansetron or vehicle were administered 2 hours prior to the injection of the antineoplastic agent and animals were observed for 5 hours. The results of these experiments are summarized in Table 5.

Table 5. Effects of Palonsetron and Ondansetron on Dacarbazine-, Actinomycin D-, and Mechlorethamine-Induced Emesis in Dogs

Treatment[a]	Dose (mg/kg)	Emetic Episodes (mean ± SD)		
		Dacarbazine (30.0 mg/kg IV)	Actinomycin D (0.15 mg/kg IV)	Mechlorethamine (0.4 mg/kg IV)
Intravenous Antiemetic				
Vehicle control[b]	0	10.33 ± 2.66	17.50 ± 11.43	10.00 ± 4.69
Palonosetron	0.001	10.17 ± 2.04	10.00 ± 0.54[c]	7.67 ± 5.05
	0.003	6.67 ± 4.13	10.83 ± 2.04	6.00 ± 4.29
	0.01	1.67 ± 1.37[d]	7.17 ± 3.06[d]	3.00 ± 3.52[d]
	0.03	0.83 ± 1.17[d]	5.17 ± 4.45[d]	0.17 ± 0.41[d]
Ondansetron	0.01	11.50 ± 5.51	7.67 ± 2.25[d]	5.83 ± 4.31
	0.03	8.17 ± 2.79	14.67 ± 4.68	3.50 ± 2.07[c]
	0.1	4.83 ± 2.48[d]	12.67 ± 3.45	5.33 ± 4.68
	0.3	1.33 ± 0.82[d]	5.83 ± 4.45[d]	4.67 ± 1.63[c]
Oral Antiemetic				
Vehicle control	0	14.17 ± 3.82	14.50 ± 5.54	9.50 ± 7.15
Palonosetron	0.003	12.83 ± 6.68	5.83 ± 1.47[d]	4.50 ± 3.51[c]
	0.01	6.83 ± 4.92[d]	6.67 ± 3.83[d]	2.83 ± 1.94[d]
	0.03	0.33 ± 0.52[d]	3.33 ± 4.55[d]	0.33 ± 0.82[d]
	0.1	0.00 ± 0.00[d]	1.00 ± 1.67[d]	0.00 ± 0.00[d]

Ondansetron	0.03	10.83 ± 2.72	9.83 ± 7.52	5.67 ± 2.50
	0.1	6.17 ± 5.35[d]	10.33 ± 4.84	8.50 ± 3.15
	0.3	3.00 ± 3.03[d]	4.20 ± 1.92[d]	2.83 ± 3.71[d]
	1	0.17 ± 0.41[d]	1.50 ± 1.38[d]	0.00 ± 0.00[d]

[a] N = Six per treatment group, except in the group receiving 0.3 mg/kg ondansetron po and actinomycin D, in which one dog was dropped due to a dosing error.
[b] Vehicle control was distilled water in each instance.
[c] Significantly less than vehicle control, $p < 0.05$.
[d] Significantly less than vehicle control, $p < 0.01$

Under the conditions of these experiments, both palonosetron and ondansetron, whether administered by the intravenous or oral route, reduced the emetic responses to all three antineoplastic agents. The antiemetic effects of both drugs were generally dose-related and palonosetron was consistently at least 10 times more potent than ondansetron.

Example 5: Human trials assessing the effectiveness of single intravenous doses of palonosetron for the prevention of highly emetogenic chemotherapy-induced nausea and vomiting.

A randomized, double-blind, multicenter, dose-ranging Phase II trial was performed to identify the dose response relationship among single I.V. doses of palonosetron. Patients receiving highly emetogenic chemotherapy including cyclophosphamide (>1100mg/m2) and cisplatin (>70mg/m2), commonly associated with delayed emesis, were assigned to one of five dose groups of a single I.V. administration of palonosetron. Palonosetron was administered alone (without dexamethasone) as a 30 second intravenous injection, 30 minutes prior to chemotherapy administration. The primary endpoint was 24-hour complete responses (no emesis, no rescue) (CR). Secondary endpoints included complete control (no emesis, no rescue, mild nausea) (CC) and 5-day CR.

161 patients (32 women, 129 men) participated. Key efficacy parameters and results are summarized in Table 6 below. A majority (83.9%) of adverse events were either mild or moderate and not attributed to study medication (86.0%). The most commonly reported adverse events related to study medication include: headache (19.3%); constipation (8.7%), dizziness (2.5%) and abdominal pain (2.5%). No serious drug-related events were reported.

The results demonstrate that in these patients, palonosetron was safe and effective in treating acute emesis and maintained activity through day 5.

Table 6

Responders by Dose

Parameters	**Palonosetron Dose (mcg/kg)**				
	0.3 - 1 (n=29)	3 (n=24)	10 (n=25)	30 (n=24)	90 (n=46)
%CR(24hr)	24	46	40	50*	46
%CC(24hr)	24	39	40	48	46
%CR(Day5)	17	17	32	33	20

*Statistically significant differences ($p<0.05$) vs. lowest dose group

Example 6: Intravenous formulation

Table 7 below presents a representative formulation of palonosetron formulated for intravenous administration.

Table 7

Ingredient	**Mg**
Palonosetron HCl	10-100 mg.
Dextrose Monohydrate Isotonic	q.s. to make
Citric Acid Monohydrate	1.05 mg.
Sodium Hydroxide	0.18 mg.
WFJ	To 1.0 ml.

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

What is claimed is:

1) A method of treating chemotherapy or radiotherapy-induced acute and delayed emesis comprising administering to an animal a treatment-effective amount of palonosetron.

2) The method of claim 1 wherein the chemotherapy or radiotherapy is defined by successive daily administrations of a chemotherapeutic agent or radiotherapy, wherein the method comprises administering palonosetron for two or more successive days.

3) The method of claim 1 wherein the chemotherapy is defined by the administration of a single dose of a delayed emesis inducing chemotherapeutic agent during a cycle of chemotherapy, wherein the method comprises administering palonosetron for two or more successive days.

4) The method of claim 1 wherein about 0.25 mg of palonosetron is administered.

5) The method of claim 1 wherein said palonosetron is administered intravenously.

6) The method of claim 1 wherein said palonosetron is administered orally.

7) The method of claim 1 comprising, in any order:

a) administering to the animal from about 3 to about 10 *u*g/kg of palonosetron; and

b) administering to the animal an emesis inducing amount of a chemotherapeutic agent.

8) The method of claim 7 wherein steps (a) and (b) are performed in sequence.

9) The method of claim 7 wherein step (a) is performed about 30 minutes prior to step (b).

10) The method of claim 1 wherein said palonosetron is administered as an intravenous bolus over a time period of about 10-30 seconds.

11) The method of claim 1 wherein about 0.25 mg of palonosetron is administered in a sterile intravenous solution comprising palonosetron at a concentration of about 0.05 mg/ml.

12) The method of claim 1 wherein about 0.25 mg of palonosetron is administered in a sterile intravenous solution comprising palonosetron at a concentration of about

0.05 mg/ml, wherein said palonosetron comprises an age of from about one month to about two years.

13) The method of claim 1 wherein said palonosetron is administered from a single unit dose ampule comprising about 0.25 mg of palonosetron in a sterile injectable solution.

14) The method of claim 1 wherein said animal is a human.

15) A method of treating chemotherapy or radiotherapy-induced emesis in an animal comprising administering a dose of 0.25 mg of palonosetron to the animal.

16) The method of claim 15 wherein the chemotherapy is defined by successive daily administrations of a chemotherapeutic agent, wherein the method comprises administering 0.25 mg. of palonosetron for two or more successive days.

17) The method of claim 15 wherein the chemotherapy is defined by the administration of a single dose of a chemotherapeutic agent and acute and delayed emesis during a cycle of chemotherapy, wherein the method comprises administering 0.25 mg. of palonosetron for two or more successive days.

18) The method of claim 15 wherein said palonosetron is administered intravenously.

19) The method of claim 15 wherein said palonosetron is administered orally.

20) The method of claim 15 wherein said palonosetron is administered as an intravenous bolus over a time period of about 10-30 seconds.

21) The method of claim 15 wherein said palonosetron is administered in a sterile intravenous solution comprising palonosetron at a concentration of about 0.05 mg/ml.

22) The method of claim 15 wherein said palonosetron is administered in a sterile intravenous solution comprising palonosetron at a concentration of about 0.05 mg/ml, wherein said palonosetron comprises an age of from about one month to about two years.

23) The method of claim 15 wherein said emesis is delayed emesis.

24) The method of claim 15 wherein said palonosetron is administered from a single unit dose ampule comprising about 0.25 mg of palonosetron in a sterile injectable solution.

25) The method of claim 15 wherein said animal is a human.

26) A method of preventing chemotherapy or radiotherapy induced emesis comprising:

a) in a first chemotherapeutic or radiotherapy session:

i) administering to a human a first amount of palonosetron; and

ii) administering to said human an emesis inducing amount of a chemotherapeutic agent or radiotherapy;

b) assessing the effectiveness of the palonosetron; and

c) in a subsequent chemotherapeutic or radiotherapy session, if said human is at least partly non-responsive to said palonosetron in said first chemotherapeutic session, administering to said animal a therapeutically effective amount of a second anti-emetic compound; and

d) wherein the subsequent chemotherapeutic session is performed without an intervening chemotherapeutic session in which a second amount of palonosetron higher than the first amount is administered.

27) A method of preventing chemotherapy or radiotherapy induced emesis comprising, in one chemotherapeutic or radiotherapy session:

a) administering to a human a first dose of palonosetron; and

b) administering to said animal an emesis inducing amount of a chemotherapeutic agent or radiotherapy;

c) assessing the effectiveness of the palonosetron; and

d) if said human is at least partly non-responsive to said first dose of palonosetron, not administering a second dose of palonosetron for at least 24 hours after step (b).

28) A single unit dose of palonosetron comprising an ampule of 0.25 mg of palonosetron in a sterile injectable solution.

29) The single unit dose of palonosetron of claim 28 wherein said palonosetron is present at a concentration of about 0.05 mg/ml.

30) The single unit dose of palonosetron of claim 28 wherein said sterile injectable solution has a pH of about 5.

31) The single unit dose of palonosetron of claim 28 wherein said palonosetron has an age of from about 1 month to about 2 years.

INTERNATIONAL SEARCH REPORT

Int onal Application No
PCT/IB 03/05567

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/473 A61P1/08

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)
IPC 7 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, PAJ, BIOSIS, EMBASE, PASCAL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	STACHER, G: "Palonosetron" CURRENT OPINION IN INVESTIGATIONAL DRUGS, vol. 3, no. 10, October 2002 (2002-10), pages 1502-1507, XP009027887	1,4-9, 14,15, 18,19, 23,25
X	page 1503, left-hand column, paragraphs 3,5 page 1503, right-hand column, paragraph 3 page 1504, left-hand column, paragraph 2 page 1505	1-31

-/--

[X] Further documents are listed in the continuation of box C.

[ ] Patent family members are listed in 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
8 April 2004	22/04/2004

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, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Albayrak, T

Form PCT/ISA/210 (second sheet) (January 2004)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EGLEN ET AL: "Pharmacological characterization of RS 25259-197, a novel and selective 5-HT-3 receptor antagonist in vivo" BRITISH JOURNAL OF PHARMACOLOGY, vol. 114, no. 4, - 1995 pages 860-866, XP009027881	1,4-9, 15,18,19
X	page 861, right-hand column, paragraphs 2,3 figure 5 table 1 page 863, left-hand column -right-hand column	1-31
X	"Palonosetron. RS 25259, RS 25259 197" DRUGS IN R&D, vol. 2, no. 4, - October 1999 (1999-10) pages 251-252, XP009027886 page 252, left-hand column, paragraph 3	1,5-7
X	SORBE, B: "5-HT3 receptor antagonists as antiemetic agents in cancer chemotherapy" EXP. OPIN. INVEST. DRUGS, vol. 5, no. 4, 1996, pages 389-407, XP009027885 page 402, left-hand column, paragraph 2	1,14
X	GASTER L M, KING F D: "Serotonin 5-HT3 and 5-HT4 Receptor Antagonists" MEDICINAL RESEARCH REVIEWS, vol. 17, no. 2, 1997, pages 163-214, XP009027880	1
X	page 167; figure 2 page 188, paragraph 5 -page 189, paragraph 1	1-31
X	PIRACCINI ET AL.: "An interesting 5-HT3 receptor antagonist antiemetic for patients undergoing chemotherapy-based conditioning regimens?" BLOOD, vol. 98, no. 11 part 2, 16 November 2001 (2001-11-16), page 350b XP009027883 Abstract Nr. 5169 the whole document	1,14

ATTORNEY DOCKET NO. 23278.20
PATENT

CERTIFICATE OF ELECTRONIC TRANSMISSION UNDER 37 C.F.R. § 1.8

I hereby certify that this correspondence, including any items indicated as attached or included, is being transmitted via electronic transmission via EFS-Web on the date indicated below.

Date: October 30, 2012

/Susan Wray/
Susan Wray

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application: **Fabio TRENTO et al.**	)	Art Unit: **1615**
Application No. **13/077,462**	)	Examiner: **Walter E. Webb**
Filed: **March 31, 2011**	)	Confirmation No.: **5608**
For: **COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING**	)	

INFORMATION DISCLOSURE STATEMENT

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

Arnall Golden Gregory LLP
Customer Number 53449

Sir:

Pursuant to the requirements of 37 C.F.R. § 1.56, submitted herewith on the accompanying Information Disclosure Statement List is a listing of documents known to Applicants and/or their attorneys. In accordance with 37 C.F.R. §1.98(a)(2), copies of any cited U.S. patent or U.S. patent application publication documents are not enclosed. Copies of any cited foreign patent document and/or any non-patent publication are enclosed.

This Information Disclosure Statement is filed in a timely manner pursuant to 37 C.F.R. § 1.97(c), in that neither a final Office Action nor a Notice of Allowance has been mailed to Applicants. Accordingly, Applicants enclose the fee required under 37 C.F.R. § 1.97(c)(2).

Applicants believe that no fees are due with this Information Disclosures Statement. However, the Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account No. 50-4667.

Respectfully submitted,

ARNALL GOLDEN GREGORY LLP

/Clark G. Sullivan/
Clark G. Sullivan
Registration No. 36,942

Arnall Golden Gregory LLP
171 17th Street NW, Suite 2100
Atlanta, Georgia 30363
Tel. 404.873.8512
Fax 404.873.8513
Customer No.: 53449

AGG Docket: 23278.20

Electronic Patent Application Fee Transmittal

Application Number:	13077462
Filing Date:	31-Mar-2011
Title of Invention:	Compositions and Methods for Treating Centrally Mediated Nausea and Vomiting
First Named Inventor/Applicant Name:	Fabio Trento
Filer:	Clark G. Sullivan/Susan Wray
Attorney Docket Number:	23278.20 (US2)

Filed as Small Entity

Utility under 35 USC 111(a) Filing Fees

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:				
Extension - 1 month with $0 paid	2251	1	75	75

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**75**

Electronic Acknowledgement Receipt

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Application Number:	13077462
International Application Number:	
Confirmation Number:	5608
Title of Invention:	Compositions and Methods for Treating Centrally Mediated Nausea and Vomiting
First Named Inventor/Applicant Name:	Fabio Trento
Customer Number:	53449
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Application Type:	Utility under 35 USC 111(a)

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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

1	Response to Election / Restriction Filed	23278_20_AMENDMENT_AND_RESPONSE_TO_RESTRICTION_REQUIREMENT.pdf	1071753 23eb3920e5f008d058b1005cff697184bc34fcd0	no	9
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:					
2	Extension of Time	23278_20_REQUEST_FOR_EXTENSION_OF_TIME.pdf	118175 e878c50fd6358ef2b26d87714bee20b9168ecb61	no	2
Warnings:					
Information:					
3	Information Disclosure Statement (IDS) Form (SB08)	23278_20_INFORMATION_DISCLOSURE_STATEMENT.pdf	712613 07668c0ba7447792bd7c077a4f073d6fb7f8bccd	no	5
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
4	Foreign Reference	23278_20_FOREIGN_PATENT_CITE_1_WO_2008_049552_A1.pdf	1530001 46e4e04a3a6d0bc60c0d48f07e9e4e1dacfbcb6a	no	36
Warnings:					
Information:					
5	Foreign Reference	23278_20_FOREIGN_PATENT_CITE_2_WO_2004_067005_A1.pdf	1143446 e0e21d3e078bf59ff3961675cc6654b64809bc06	no	27
Warnings:					
Information:					
6	Foreign Reference	23278_20_FOREIGN_PATENT_CITE_3_WO_2004_073714_A1.pdf	1886985 e89317e3b93a6c63c256b08922d54464ef578cc4	no	39
Warnings:					
Information:					
7	Foreign Reference	23278_20_FOREIGN_PATENT_CITE_4_WO_2004_045615_A1.pdf	1502124 8cb203aba43aea229ac9f9d81e8477a5e8f6d18a	no	29
Warnings:					
Information:					
8	Non Patent Literature	23278_20_NON_PATENT_LITERATURE_CITE_1_EMEND.pdf	2079986 4720f12ca55969e6e424b5564a3055f72dbb1277	no	15
Warnings:					
Information:					

9	Non Patent Literature	23278_20_NON_PATENT_LITERATURE_CITE_2_RUHLMANN.pdf	2743195 32c57ee9f8d97e4fd6bc4551a371a38125218317	no	10
Warnings:					
Information:					
10	Non Patent Literature	23278_20_NON_PATENT_LITERATURE_CITE_3_PELLEGATTI.pdf	2864602 7743e914e90e8aab73db2404039a029027976a34	no	11
Warnings:					
Information:					
11	Non Patent Literature	23278_20_NON_PATENT_LITERATURE_CITE_4_HUANG.pdf	4414657 49852e9b0b409cc6847c92dd3ecb6cf3d0ba2219	no	27
Warnings:					
Information:					
12	Non Patent Literature	23278_20_NON_PATENT_LITERATURE_CITE_5_REDDY.pdf	538360 a7a88e348d1e728f68aadd96bd65df607ad05ceb	no	3
Warnings:					
Information:					
13	Non Patent Literature	23278_20_NON_PATENT_LITERATURE_CITE_6_DE_WIT.pdf	1179563 029a21d9fbcff25a3a991b3016376ab20a1ea5a0	no	5
Warnings:					
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14	Non Patent Literature	23278_20_NON_PATENT_LITERATURE_CITE_7_DIEMUNSCH_NEUROKININ.pdf	1447368 4eede7c85962aebf9b3c164023d0f2bd8a9db67d	no	7
Warnings:					
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15	Non Patent Literature	23278_20_NON_PATENT_LITERATURE_CITE_8_DIEMUNSCH_POTENTIAL.pdf	2101214 90ac339463f3d6f08f263bb126a210684409a59e	no	20
Warnings:					
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16	Non Patent Literature	23278_20_NON_PATENT_LITERATURE_CITE_9_GRUNBERG.PDF	811784 5880c7e3daa67faf01c95bb41cd7bc67a9fa0810	no	6
Warnings:					
Information:					
17	Non Patent Literature	23278_20_NON_PATENT_LITERATURE_CITE_10_STATHIS.pdf	946181 41a976048e1366efdb4263e90e9917db958a7ba8	no	6
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:					
18	Transmittal Letter	23278_20_INFORMATION_DISCLOSURE_STATEMENT_TRANSMITTAL.pdf	127151 9ed22d9c0978a9119488f31fabd7492ffb39490a	no	2
Warnings:					
Information:					
19	Fee Worksheet (SB06)	fee-info.pdf	30191 29fa169e6eff94242c300172f43a76d201eda75e	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	27249349	

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.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/077,462	03/31/2011	Fabio Trento	23278.20 (US2)	5608

53449 7590 11/20/2012

PATENT CORRESPONDENCE
ARNALL GOLDEN GREGORY LLP
171 17TH STREET NW
SUITE 2100
ATLANTA, GA 30363

EXAMINER	
WEBB, WALTER E	

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
11/20/2012	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):

patents@agg.com

Office Action Summary	Application No.	Applicant(s)	
	13/077,462	TRENTO ET AL.	
	Examiner	Art Unit	
	WALTER WEBB	1612	

-- 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* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, 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 *30 October 2012*.

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

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

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

Disposition of Claims

5)☒ Claim(s) *1-51* is/are pending in the application.

5a) Of the above claim(s) *34-49* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-3, 16-18 and 27-29* is/are rejected.

8)☒ Claim(s) *4-15,19-26,28-33,50 and 51* 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).

a)☐ All b)☐ Some * c)☐ None of:

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/08) Paper No(s)/Mail Date *10/30/2012*.

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

4) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election of Invention I, claims 1-33, in the reply filed on 10/30/2012 is acknowledged. Although **no election of species was required**, applicant further elected "the treatment of CINV for five consecutive days by administering on day one 0.5 mg of palonosetron, 300 mg of netupitant, and 12 mg of dexamethasone, wherein no further netupitant or palonosetron is administered during the five days" (p. 1). Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 34-49 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Note: In applicant's response, claims 50 and 51 were not grouped with invention I, as indicated in the Restriction requirement filed 9/28/2012. If applicant means to withdraw claims 50 and 51, the Examiner recommends submitting a new claim set indicating claims 50 and 51 as withdrawn.

Specification

Applicant is reminded of the proper content of an abstract of the disclosure.

A patent abstract is a concise statement of the technical disclosure of the patent and should include that which is new in the art to which the invention pertains. If the patent is of a basic nature, the entire technical disclosure may be new in the art, and the abstract should be directed to the entire disclosure. If the patent is in the nature of an improvement in an old apparatus, process, product, or composition, the abstract should include the technical disclosure of the improvement. In certain patents, particularly

those for compounds and compositions, wherein the process for making and/or the use thereof are not obvious, the abstract should set forth a process for making and/or use thereof. If the new technical disclosure involves modifications or alternatives, the abstract should mention by way of example the preferred modification or alternative.

The abstract should not refer to purported merits or speculative applications of the invention and should not compare the invention with the prior art.

Where applicable, the abstract should include the following:
(1) if a machine or apparatus, its organization and operation;
(2) if an article, its method of making;
(3) if a chemical compound, its identity and use;
(4) if a mixture, its ingredients;
(5) if a process, the steps.

Extensive mechanical and design details of apparatus should not be given.

The abstract of the disclosure is objected to because it is drawn to methods and compositions and does not include method steps or components for the compositions. Correction is required. See MPEP § 608.01(b).

Claim Objections

Claims 50 and 51 are 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. Claims 50 and 51 are improper insofar as they depend from a withdrawn claim, i.e. claim 34. Claims 50 and 51 are also improper because a multiple dependent claim cannot depend from any other multiple dependent claim. See MPEP § 608.01(n). Accordingly, the claims have not been further treated on the merits.

Claim 1 is objected to because of the following informalities: abbreviations "NK_1" and "5-HT_3" should be initially spelled out to avoid confusion. Also "netupinant" is misspelled. Appropriate correction is required.

Claims 4-15, 19-26, 30-33 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from any other multiple dependent claim. See MPEP § 608.01(n). Accordingly, the claims have not been further treated on the merits.

Claim 6, 7, 11, 12, 14, 15, 20-22, 28, 29 and 31 are objected to because of the following informalities: there is a period (.) after "mg". Appropriate correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 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 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 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3, 16-18 and 27-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reddy et al., (Supportive Cancer Therapy, cited in IDS).

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). 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). Consequently, 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. Accordingly, the artisan would have reasonably expected enhanced treatment of CINV with netupitant.

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)

Reddy et al. is not anticipatory insofar as netupitant is not a preferred species. However, it would have been obvious to select netupitant given its plain enumeration in the prior art reference.

In regard to claims 2, where dexamethasone is administered on days two, three and four, claims 28-29, wherein netupitant comprises from about 200 to about 400mg, and palonosetron is from about 0.25 to about 0.75 mg, it would have been obvious to optimize when and how much dexamethasone, netupitant, and palonosetron is administered, 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.

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

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

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT
(Not for submission under 37 CFR 1.99)

Application Number	13077462
Filing Date	2011-03-31
First Named Inventor	Trento, Fabio
Art Unit	1612
Examiner Name	Webb, Walter E.
Attorney Docket Number	23278.20

U.S.PATENTS

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, III et al.	
	3	6297375		2001-10-02	Bös 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.

U.S.PATENT APPLICATION PUBLICATIONS

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					

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FOREIGN PATENT DOCUMENTS

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /W.W./

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	13077462
Filing Date	2011-03-31
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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	WO 2008/049552 A1			2008-05-02	Helsinn Healthcare SA		☐
	2	WO 2004/067005 A1			2004-08-12	Helsinn Healthcare SA		☐
	3	WO 2004/073714 A1			2004-09-02	Helsinn Healthcare SA		☐
	4	WO 2004/045615 A1			2004-06-03	Helsinn Healthcare SA		☐

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NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	March 27, 2003, Approved FDA Prescribing Information for Emend	☐
	2	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	☐
	3	PELLEGATTI, MARIO et al., "Disposition and Metabolism of Radiolabeled Casopitant in Humans," Drug Metabolism and Disposition, vol. 37, no. 8, 2009, pp.1635-1645	☐
	4	HUANG, SHIH-CHUNG et al., "Neurokinin-1 receptor antagonists: a comprehensive patent survey," Expert Opin. Ther. Patents (2010) 20(8), pp. 1019-1045	☐

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /W.W./

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	13077462
	Filing Date	2011-03-31
	First Named Inventor	Trento, Fabio
	Art Unit	1612
	Examiner Name	Webb, Walter E.
	Attorney Docket Number	23278.20

	5	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	☐
	6	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	☐
	7	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	☐
	8	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	☐
	9	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	☐
	10	STATHIS, MARIGO et al., "Inhibition of substance P-mediated responses in NG108-15 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

EXAMINER SIGNATURE

Examiner Signature	/Walter Webb/	Date Considered	11/13/2012

*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./

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	0	netupinant	USPAT	OR	OFF	2012/11/13 14:56
L2	1	netupinant	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2012/11/13 14:57
L3	555	dexamethasone palonosetron	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2012/11/13 14:59
L4	10	dexamethasone palonosetron	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	NEAR	ON	2012/11/13 14:59
L5	206	dexamethasone palonosetron	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2012/11/13 14:59
L6	7679	neurokinin	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2012/11/13 15:00
L7	206	l5 and l3	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2012/11/13 15:00
L8	52	l7 and l6	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2012/11/13 15:00
L9	52311	emesis or nausea or vomiting	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2012/11/13 15:02
L10	42	l8 and l9	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2012/11/13 15:02
L11	49	netupitant	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2012/11/13 15:05
L12	22	l11 and l9	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2012/11/13 15:07
L13	17	R-1124	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2012/11/13 15:10

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BIB DATA SHEET

CONFIRMATION NO. 5608

SERIAL NUMBER	FILING or 371(c) DATE RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
13/077,462	03/31/2011	424	1612	23278.20 (US2)

APPLICANTS

Fabio Trento, Pare (Como), ITALY;
Sergio Cantoreggi, Cagiallo, SWITZERLAND;
Giorgia Rossi, Cernobbio (Como), ITALY;
Roberta Cannella, Varese, ITALY;
Daniele Bonadeo, Casalzuigno, ITALY;
Riccardo Braglia, Lugano-Pazzallo, SWITZERLAND;

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

This appln claims benefit of 61/382,709 09/14/2010

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

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED **** ** SMALL ENTITY **
04/13/2011

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	51	5

ADDRESS

PATENT CORRESPONDENCE
ARNALL GOLDEN GREGORY LLP
171 17TH STREET NW
SUITE 2100
ATLANTA, GA 30363
UNITED STATES

TITLE

Compositions and Methods for Treating Centrally Mediated Nausea and Vomiting

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Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13077462	TRENTO ET AL.
	Examiner	Art Unit
	WALTER WEBB	1612

SEARCHED			
Class	Subclass	Date	Examiner
514	218	11/13/2012	WW

SEARCH NOTES		
Search Notes	Date	Examiner
Inventors Name Search on PALM	11/13/2012	WW
EAST Search History	11/13/2012	WW
NPL Search Terms: palonosetron, dexamethasone, netupinant, neurokinin-1, emesis, nausea, vomiting	11/13/2012	WW

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner

UNITED STATES PATENT AND TRADEMARK OFFICE
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PATENT CORRESPONDENCE
ARNALL GOLDEN GREGORY LLP
171 17TH STREET NW
SUITE 2100
ATLANTA, GA 30363

Courtesy Reminder for
Application Serial No: 13/077,462

Attorney Docket No: 23278.20 (US2)
Customer Number: 53449
Date of Electronic Notification: 11/20/2012

This is a courtesy reminder that new correspondence is available for this application. The official date of notification of the outgoing correspondence will be indicated on the form PTOL-90 accompanying the correspondence.

An email notification regarding the correspondence was sent to the following email address(es) associated with your customer number:
patents@agg.com
Please verify that these email addresses are correct.

To view your correspondence online or update your email addresses, please visit us anytime at **https://sportal.uspto.gov/secure/myportal/privatepair.** If you have any questions, please email the Electronic Business Center (EBC) at EBC@uspto.gov or call 1-866-217-9197.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application:		)	
		)	
Fabio Trento et al.		)	Examiner: Walter E. Webb
		)	
Serial No.	13/077,462	)	Art Unit: 1612
		)	
Filed:	March 31, 2011	)	Confirmation No.: 5608
		)	
For:	Compositions and Methods for Treating Centrally Mediated Nausea and Vomiting	)	

CORRECTION OF INVENTORSHIP UNDER 35 U.S.C. §116 AND 37 C.F.R. §1.48

Commissioner of Patents
United States Patent Office
Alexandria, Virginia

Arnall Golden Gregory LLP
Customer Number 53449

Dear Sir:

Please accept this request to correct inventorship under 35 U.S.C. 116 and 37 C.F.R. 1.48. Riccardo Braglia was listed as an inventor of this application in error. A statement from each individual being removed as an inventor from this application that the error in inventorship occurred with no deceptive intent on his part is filed herewith. A corrected Application Data Sheet, a declaration by the actual inventors, the processing fee set forth in 37 C.F.R. 1.17(i), the written consent of the assignee, and the statement under 37 C.F.R. 3.73(b) are also enclosed herewith.

Respectfully submitted,

ARNALL GOLDEN GREGORY LLP

/Clark G. Sullivan/
Clark G. Sullivan
Registration No. 36,942

February 21, 2013

ARNALL GOLDEN GREGORY LLP
(404) 873-8500
(404) 873-8501 (fax)
Customer No.: 53449

AGG Docket No.: 23278.20.US.2

PTO/SB/14 (11-08)
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 contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	23278.20
	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.)

Applicant Information:

Applicant 1

Applicant Authority	◉ Inventor	○ Legal Representative under 35 U.S.C. 117	○ Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
	Fabio		Trento	

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

City	Como	Country Of Residence	IT
Citizenship under 37 CFR 1.41(b)	IT		

Mailing Address of Applicant:

Address 1	Via Alla Valle 20B		
Address 2	Paré		
City	Como	State/Province	
Postal Code	I-22020	Country	IT

Applicant 2

Applicant Authority	◉ Inventor	○ Legal Representative under 35 U.S.C. 117	○ Party of Interest under 35 U.S.C. 118

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	CH
Citizenship under 37 CFR 1.41(b)	CH		

Mailing Address of Applicant:

Address 1	Via Sarone 21A		
Address 2			
City	Cagiallo	State/Province	
Postal Code	CH6955	Country	CH

Applicant 3

Applicant Authority	◉ Inventor	○ Legal Representative under 35 U.S.C. 117	○ Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
	Giorgia		Rossi	

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

City	Como	Country Of Residence	IT

PTO/SB/14 (11-08)
Approved for use through 01/31/2014. OMB 0651-0032
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	23278.20
	Application Number	
Title of Invention	Compositions and Methods for Treating Centrally Mediated Nausea and Vomiting	

Citizenship under 37 CFR 1.41(b)	IT				
Mailing Address of Applicant:					
Address 1	Via della Libertá, 1A				
Address 2	Cernobbio				
City	Como	**State/Province**			
Postal Code	I-22012	**Country**	IT		

Applicant 4

Applicant Authority	(•) Inventor	( ) Legal Representative under 35 U.S.C. 117	( ) Party of Interest under 35 U.S.C. 118	
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**	IT		
Citizenship under 37 CFR 1.41(b)	IT				
Mailing Address of Applicant:					
Address 1	Via Al Colle, 42				
Address 2					
City	Varese	**State/Province**			
Postal Code	I-21100	**Country**	IT		

Applicant 5

Applicant Authority	(•) Inventor	( ) Legal Representative under 35 U.S.C. 117	( ) Party of Interest under 35 U.S.C. 118	
Prefix	**Given Name**	**Middle Name**	**Family Name**	**Suffix**
	Daniele		Bonadeo	

Residence Information (Select One)	( ) US Residency	(•) Non US Residency	( ) Active US Military Service		
City	Varese	**Country Of Residence**	IT		
Citizenship under 37 CFR 1.41(b)	IT				
Mailing Address of Applicant:					
Address 1	Via Ronco Capo Caccia, 32				
Address 2	Casalzuigno				
City	Varese	**State/Province**			
Postal Code	I-21030	**Country**	IT		

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	53449

PTO/SB/14 (11-08)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	23278.20
	Application Number	
Title of Invention	Compositions and Methods for Treating Centrally Mediated Nausea and Vomiting	

Email Address	patents@agg.com	Add Email	Remove Email

Application Information:

Title of the Invention	Compositions and Methods for Treating Centrally Mediated Nausea and Vomiting		
Attorney Docket Number	23278.20	**Small Entity Status Claimed**	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Suggested Class (if any)		**Sub Class (if any)**	
Suggested Technology Center (if any)			
Total Number of Drawing Sheets (if any)		**Suggested Figure for Publication (if any)**	

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). Enter either Customer Number or complete the Representative Name section below. If both sections are completed the Customer Number will be used for the Representative Information during processing.

Please Select One:	◉ Customer Number	○ US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	53449		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, or 365(c) or indicate National Stage entry from a PCT application. Providing this 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(a)(2) or CFR 1.78(a)(4), and need not otherwise be made part of the specification.

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	Continuation of	PCT/US10/57192	2010-11-19
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
PCT/US10/57192	non provisional of	61382709	2010-09-14
Prior Application Status	Expired		Remove

PTO/SB/14 (11-08)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	23278.20
	Application Number	
Title of Invention	Compositions and Methods for Treating Centrally Mediated Nausea and Vomiting	

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
PCT/US10/57192	non provisional of	61262470	2009-11-18

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

Foreign Priority Information:

This section allows for the applicant to claim benefit of foreign priority and to identify any prior foreign application for which priority is not claimed. 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(a).

Remove

Application Number	Country[i]	Parent Filing Date (YYYY-MM-DD)	Priority Claimed
			◉ Yes ○ No

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

Assignee Information:

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

Assignee 1

If the Assignee is an Organization check here. ☒

Organization Name	Helsinn Healthcare S.A.		
Mailing Address Information:			
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 Data may be generated within this form by selecting the **Add** button.

Signature:

A signature of the applicant or representative is required in accordance with 37 CFR 1.33 and 10.18. Please see 37 CFR 1.4(d) for the form of the signature.

Signature	/Clark G. Sullivan/			Date (YYYY-MM-DD)	2013-02-21
First Name	Clark G.	Last Name	Sullivan	Registration Number	36942

PTO/SB/14 (11-08)
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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	23278.20
	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 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.

STATEMENT OF RICCARDO BRAGLIA TO CORRECT INVENTORSHIP
UNDER 37 C.F.R. §1.48(a)(2)

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 33213-1450

1. I am Riccardo Braglia of Via Pian Scairolo 9, CH-6912, Pazzallo, Switzerland.

2. I have been listed as an inventor in error on U.S. Application No. 13/077,462.

3. I consent to be removed as an inventor on the above-listed application.

4. This error in inventorship occurred without any deceptive intent on my part.

Riccardo Braglia

09/10/2012
Date

4825147v1

Electronic Patent Application Fee Transmittal

Application Number:	13077462
Filing Date:	31-Mar-2011
Title of Invention:	Compositions and Methods for Treating Centrally Mediated Nausea and Vomiting
First Named Inventor/Applicant Name:	Fabio Trento
Filer:	Clark G. Sullivan/Susan Wray
Attorney Docket Number:	23278.20 (US2)

Filed as Small Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Petition fee- 37 CFR 1.17(h) (Group III)	1464	1	130	130
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**130**

Electronic Acknowledgement Receipt

EFS ID:	15020657
Application Number:	13077462
International Application Number:	
Confirmation Number:	5608
Title of Invention:	Compositions and Methods for Treating Centrally Mediated Nausea and Vomiting
First Named Inventor/Applicant Name:	Fabio Trento
Customer Number:	53449
Filer:	Clark G. Sullivan/Susan Wray
Filer Authorized By:	Clark G. Sullivan
Attorney Docket Number:	23278.20 (US2)
Receipt Date:	21-FEB-2013
Filing Date:	31-MAR-2011
Time Stamp:	18:49:55
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$130
RAM confirmation Number	6185
Deposit Account	504667
Authorized User	BERMAN, RONNA
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Request under Rule 48 correcting inventorship	23278_20_US2_CORRECTION_OF_INVENTORSHIP_UNDER_35_USC_116_AND_37_CFR_1_48.pdf	88426 741912028bf96de72458d02e3551e60855cf338c	no	2
Warnings:					
Information:					
2	Application Data Sheet	23278_20_US2_APPLICATION_DATA_SHEET.pdf	861000 dd7dcebb88a12c7605ba2701c517010bc8f0b0d4	no	6
Warnings:					
Information:					
This is not an USPTO supplied ADS fillable form					
3	Oath or Declaration filed	23278_20_US2_DECLARATION_AND_POWER_OF_ATTORNEY.pdf	316436 75667b1e22c141fa692538d3a934637f9df03e5d	no	6
Warnings:					
Information:					
4	Request under Rule 48 correcting inventorship	23278_20_US2_STATEMENT_OF_ASSIGNEE_TO_CORRECT_INVENTORSHIP_UNDER_37_CFR_1_48.pdf	46123 7d3db2f23effd74f6d479729ae76b7e081be2ae5	no	1
Warnings:					
Information:					
5	Request under Rule 48 correcting inventorship	23278_20_US2_STATEMENT_OF_ASSIGNEE_TO_CORRECT_INVENTORSHIP_UNDER_37_CFR_3_73.pdf	142829 a8485097cdb8d56f2f14056ce519b4c558ccba02	no	1
Warnings:					
Information:					
6	Request under Rule 48 correcting inventorship	23278_20_US2_STATEMENT_TO_CORRECT_INVENTORSHIP.pdf	37975 26af66d427ed7c9fc5ab0cca2fde1a3d3ed3fae9	no	1
Warnings:					
Information:					
7	Fee Worksheet (SB06)	fee-info.pdf	30069 69122a743f21aa9651994cf158749558a711b905	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	1522858		

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.

In re Application of: **Fabio TRENTO, Sergio CANTOREGGI, Giorgia ROSSI, Roberta CANNELLA, and Daniele BONADEO**

As a below named inventor, I hereby declare that my residence, post office address and citizenship are as stated below next to my name. I believe I am an original, first and joint inventor of the subject matter which is claimed and for which a patent is sought on the invention entitled **"COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING"**, the specification of which was filed in U.S. Application No. 13/077,462 filed **March 31, 2011.**

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above. I do not know and do not believe that the same was ever known or used by others in the United States of America before my or our invention thereof, or patented or described in any printed publication in any country before my or our invention thereof or more than one year prior to the date of this application. I further state that the invention was not in public use or on sale in the United States of America more than one year prior to the date of this application. *I understand that I have a duty of candor and good faith toward the Patent and Trademark Office,* and I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, § 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, § 119 (a)-(d) of the foreign application(s) for patent or inventor's certificate listed below, and have also identified below any foreign application for patent or inventor's certificate disclosing subject matter in common with the above-identified specification and having a filing date before that of the application on which priority is claimed:

Application No.	Country	Filing Date	Priority Claimed Under 35 USC § 119 (a)-(d)

I hereby claim the benefit under Title 35, United States Code, § 119(e) of any United States provisional application(s) listed below:

(Application No.)	(Filing Date)	(Application No.)	(Filing Date)
61/262,470	**November 18, 2009**	**61/382,709**	**September 14, 2010**

I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s) listed below and, insofar as the subject matter disclosed and claimed in the present application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code § 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, § 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application:

Application Serial No.	Filing Date	Status: patented, pending, abandoned
PCT/US10/57192	**November 19, 2010**	**Pending**

I further 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 statement 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 patents issuing thereon.

POWER OF ATTORNEY: I hereby appoint Clark G. Sullivan, Reg. No. 36,942, in addition to the practitioners associated with Customer Number **53449** to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith.

Send correspondence to: Clark G. Sullivan
Arnall Golden Gregory LLP
Customer No. 53449
171 17th Street, Suite 2100
Atlanta, Georgia 30363

Direct telephone calls to **(404) 873-8512**

Full name of first inventor: **Fabio TRENTO**	Citizenship: Italy
Inventor's signature	Date: 09 | 10 | 2012
Residence and Post Office Address: **Via Alla Valle 20B I-22020 Parè (Como - Italy)**	

Full name of second inventor: **Sergio CANTOREGGI**	Citizenship: Switzerland
Inventor's signature	Date: 09/10/2012
Residence and Post Office Address: **Via Sarone 21A, Cagiallo, CH6955, Switzerland**	

Full name of second inventor: **Giorgia ROSSI**	Citizenship: Italy
Inventor's signature Giorgia Rossi	Date: 09 10 2012
Residence and Post Office Address: **Via della Libertà, 1A - I-22012 Cernobbio (Como - Italy)**	

Full name of second inventor: **Roberta CANNELLA**	Citizenship: Italy
Inventor's signature Roberta Cannella	Date: 09/10/2012
Residence and Post Office Address: **Via Al Colle, 42 - I-21100 Varese, Italy**	

Full name of second inventor: **Daniele BONADEO**	Citizenship: Italy
Inventor's signature Daniele Bonadeo	Date: 09/10/2019
Residence and Post Office Address: **Via Ronco Capo Caccia, 32 - I-21030 Casalzuigno, Varese, Italy**	

PTO/SB/96 (07-09)
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STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: Helsinn Healthcare S.A.

Application No./Patent No.: 13/077,462 Filed/Issue Date: 3/31/2011

Titled: Combined Oral Dosage Forms of Palonosetron and Netupitant

Helsinn Healthcare S.A. , a corporation

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

states that it is:

1. ☒ the assignee of the entire right, title, and interest in;

2. ☐ an assignee of less than the entire right, title, and interest in (The extent (by percentage) of its ownership interest is _____ %); or

3. ☐ the assignee of an undivided interest in the entirety of (a complete assignment from one of the joint inventors was made)

the patent application/patent identified above, by virtue of either:

A. ☒ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel 026059, Frame 0473, or for which a copy therefore is attached.

OR

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

1. From: _____ To: _____

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

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

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

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

Signature	Date: 9 October 2012
Matteo Missaglia	
Senior Director, Legal Affairs	
Printed or Typed Name	Title

This collection of information is required by 37 CFR 3.73(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.**

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STATEMENT OF ASSIGNEE CONSENTING TO CHANGE IN INVENTORSHIP IN PATENT APPLICATION UNDER 37 C.F.R. 1.48(a)(5)

1. Helsinn Healthcare S.A. is the assignee of U.S. Patent Application No. 13/077,462.

2. Riccardo Braglia was listed in error as an inventor in U.S. Patent Application No. 13/077,462.

3. Helsinn Healthcare S.A. consents to the removal of Riccardo Braglia as an inventor on the above-listed patent application.

Helsinn Healthcare S.A.

Print Name: Matteo Missaglia
Title: Senior Director, Legal Affairs

09/10/2012
Date

5288161v1

Electronic Acknowledgement Receipt

EFS ID:	15020657
Application Number:	13077462
International Application Number:	
Confirmation Number:	5608
Title of Invention:	Compositions and Methods for Treating Centrally Mediated Nausea and Vomiting
First Named Inventor/Applicant Name:	Fabio Trento
Customer Number:	53449
Filer:	Clark G. Sullivan/Susan Wray
Filer Authorized By:	Clark G. Sullivan
Attorney Docket Number:	23278.20 (US2)
Receipt Date:	21-FEB-2013
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Adjustment date: 02/28/2013 ABALINAN
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Authorized User	BERMAN, RONNA
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)	

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
13/077,462	03/31/2011	1612	1878	23278.20 (US2)	51	5

CONFIRMATION NO. 5608

REPLACEMENT FILING RECEIPT

53449
PATENT CORRESPONDENCE
ARNALL GOLDEN GREGORY LLP
171 17TH STREET NW
SUITE 2100
ATLANTA, GA 30363



Date Mailed: 03/06/2013

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 (Como), ITALY;
Sergio Cantoreggi, Cagiallo, SWITZERLAND;
Giorgia Rossi, Cernobbio (Como), ITALY;
Roberta Cannella, Varese, ITALY;
Daniele Bonadeo, Casalzuigno, ITALY;

Applicant(s)

Fabio Trento, Pare (Como), ITALY;
Sergio Cantoreggi, Cagiallo, SWITZERLAND;
Giorgia Rossi, Cernobbio (Como), ITALY;
Roberta Cannella, Varese, ITALY;
Daniele Bonadeo, Casalzuigno, ITALY;

Assignment For Published Patent Application

HELSINN HEALTHCARE SA, Pambio-Noranco (Lugano), SWITZERLAND

Power of Attorney: The patent practitioners associated with Customer Number 53449

Domestic Priority data as claimed by applicant

This appln 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.

If Required, Foreign Filing License Granted: 04/13/2011

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 13/077,462**

Projected Publication Date: Not Applicable

Non-Publication Request: No

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

Compositions and Methods for Treating Centrally Mediated Nausea and Vomiting

Preliminary Class

424

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application:	)	
	)	
Fabio TRENTO *et al.*	)	Examiner: Walter E. Webb
	)	
Serial No.: 13/077,462	)	Art Unit: 1612
	)	
Filed: March 31, 2011	)	Confirmation No.: 5608
	)	
For: Compositions and Methods for Treating Centrally Mediated Nausea and Vomiting	)	

AMENDMENT AND RESPONSE TO OFFICE ACTION

Commissioner of Patents
United States Patent Office
Alexandria, Virginia

Arnall Golden Gregory LLP
Customer Number 53449

Dear Sir:

In response to the Official Action mailed November 20, 2012, please enter the following amendments and consider the following remarks. Enclosed herewith is a petition for three-month extension of time along with the associated fee (small entity). Also enclosed is a Declaration under 37 C.F.R. § 132 from Giorgia Rossi and Claudio Pietra, and an Information Disclosure Statement and Form SB08 listing of references.

Amendments to the specification begin on page 2.

Amendments to the claims begin on page 3.

Remarks/Arguments begin on page 8.

AMENDMENTS TO THE SPECIFICATION

Please replace the abstract with the following abstract paragraph, shown in mark-up version to clarify amendments to the text.

Provided are ~~compositions and~~ methods for treating nausea and vomiting in patients undergoing chemotherapy, radiotherapy, or surgery, comprising the co-administration of netupitant, palonosetron and dexamethasone.

REPLACEMENT CLAIM SET

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

a) administering to said patient on day one ~~netupinant~~ 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 neurokinin-1 (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 palonosetron ~~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 chemotherapy induced nausea and vomiting (CINV) when administered alone, but effective against CINV ~~nausea and vomiting~~ when administered in combination with said netupitant,

wherein said first dose of dexamethasone comprises from 50 to 70% of a minimum effective dose when administered alone against CINV;

steps (a), (b) and (c) are effective to treat both nausea and vomiting during the period defined by days one through five; and

steps (a), (b) and (c) are effective to treat both nausea and vomiting to a greater extent during the period defined by days one through five than steps (b) and (c) alone.

2) (CURRENTLY AMENDED) 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 against vomiting, but effective against ~~nausea and~~ vomiting when administered in

combination with steps (a) and (b) ~~said netupitant~~, wherein said second dose comprises from 40 to 60% of a minimum effective dose when administered alone against vomiting.

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

5) (CURRENTLY AMENDED) The method of ~~any one of claims 1 to 4~~ claim 1, 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) (CURRENTLY AMENDED) The method of ~~any one of claims 1 to 5~~ claim 1, wherein said therapeutically effective amount of netupitant comprises from about 200 to about 400 ~~mg.~~ mg of netupitant or a pharmaceutically acceptable salt thereof.

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

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

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

10) (CANCELED)

11) (CURRENTLY AMENDED) The method of ~~any one of claims 1 to 10~~ claim 1, wherein said therapeutically effective amount of ~~5-HT_3 antagonist~~ palonosetron or pharmaceutically acceptable salt thereof is ~~comprises~~ from about 0.25 to about 0.75 ~~mg.~~ mg based on the weight of the free base ~~of palonosetron or a pharmaceutically acceptable salt thereof~~.

12) (CURRENTLY AMENDED) The method of ~~any one of claims 1 to 11~~ claim 1, wherein said palonosetron is administered as palonosetron hydrochloride, and said therapeutically effective amount of said palonosetron hydrochloride is ~~5-HT$_3$ antagonist comprises~~ about 0.56 ~~mg.~~ mg of palonosetron hydrochloride, corresponding to about 0.5 mg of palonosetron as a free base.

13) (CURRENTLY AMENDED) The method of ~~any one of claims 1 to 12~~ claim 1, wherein said palonosetron is administered orally.

14) (CURRENTLY AMENDED) The method of ~~any one of claims 1 to 13~~ claim 1, comprising orally administering:

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

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

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

15) (CURRENTLY AMENDED) The method of ~~any one of claims 1 to 14~~ claim 1, comprising orally administering:

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

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

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

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

16)-22) (CANCELED)

23) (CURRENTLY AMENDED) The method of claim 1 ~~any one of claims 1-25~~, 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 1 ~~any one of claims 1-25~~, wherein said nausea and vomiting is induced by moderately or highly emetogenic chemotherapy.

25) (CURRENTLY AMENDED) The method of claim 1 ~~any one of claims 1-25~~, 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 1 ~~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) (CURRENTLY AMENDED) A method of treating both nausea and vomiting in a human subject in need thereof during the acute or ~~and/or~~ delayed phases of chemotherapy induced nausea and vomiting (CINV) in response to moderately or highly emetogenic chemotherapy, comprising administering to said subject before said chemotherapy 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) (CURRENTLY AMENDED) The method of claim 27, comprising orally administering from about 200 to about 400 ~~mg.~~ mg of netupitant or a pharmaceutically acceptable salt thereof, and from about 0.25 to about 0.75 ~~mg.~~ mg of palonosetron or a pharmaceutically acceptable salt thereof.

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

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

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

32)-51) (CANCELED)

52) (NEW) The method of claim 1, wherein said netupitant or pharmaceutically acceptable salt thereof and said palonosetron or pharmaceutically acceptable salt thereof are synergistically effective to antagonize NK1 activity.

53) (NEW) The method of claim 27, wherein said netupitant or pharmaceutically acceptable salt thereof and said palonosetron or pharmaceutically acceptable salt thereof are synergistically effective to antagonize NK1 activity.

REMARKS

Claims 1-9, 11-15, 23-31, 52 and 53 are pending in the application. Claims 10, 16-22, and 32-51 are canceled. Claims 1, 2, 4-9, 11-15, 23-31 are amended; new claims 52 and 53 are added. The claims are amended for clarification and to:

- distinguish between nausea, vomiting, and CINV, to make clear that nausea is a separate target of the therapy from vomiting; nausea is treated under the claims whenever the incidence of nausea or significant nausea is reduced at any time point during the acute or delayed phases of CINV.
- emphasize the ability of netupitant to treat nausea when added to a regimen of palonosetron and dexamethasone (claim 1) (support at, inter alia, Table 6).
- emphasize the synergy observed from the combination of netupitant and palonosetron when treating CINV (claims 52 and 53) (support at, inter alia, pages 2 and 3)

No new matter is added by the amendments.

Elections/Restrictions

Applicants thank the Examiner for pointing out the omission regarding the election of claims 50 and 51 in the most recent response. Applicants clarify herewith that the elected claims are 1-33, and do not include claims 50 or 51.

Specification

The Office action objects to the abstract of the disclosure under MPEP § 608.01(b) and required correction on the ground that the abstract does not include method steps or components for the compositions. Applicants submit herewith a replacement paragraph that is believed to comply with the requirements of MPEP § 608.01(b) and with MPEP § 714 at section II.B.

Claim Objections

The Office action objects to claims 50 and 51 under 37 CFR 1.75(c) and MPEP § 608.01(h) as being of improper form because they depend from a withdrawn claim and because multiple dependent claim 50 (from which claim 51 depends) is dependent from other multiple dependent claims. Claims 50 and 51 have been cancelled, which we trust has overcome the objection.

Claim 1 is objected to because of the following informalities: abbreviations "NK1" and "5-HT3" were not initially spelled out, and "netupitant" was misspelled. Claim 1 has been amended to correct these informalities, as have claim 16 and claim 27.

Claims 4-15, 19-26, and 30-33 are objected to under 37 CFR 1.75(c) as multiple dependent claims depending from another multiple claim. All multiple dependencies in the claims have been removed.

Claims 6, 7, 11, 12, 14, 15, 20-22, 28, 29 and 31 are objected to because of a period after "mg". Those claims have been amended to correct this informality, in addition to claim 16.

Claim Rejections – 35 U.S.C. § 103

Claims 1-3, 16-18 and 27-29 are rejected under 35 U.S.C. 103(a) as obvious over Reddy *et al.* ("Novel Neurokinin-1 Antagonists as Antiemetics for the Treatment of Chemotherapy-Induced Emesis," *Supportive Cancer Therapy*, 3(3):140-142 (2006)). According to the Office action, it would have been obvious to combine netupitant, palonosetron and dexamethasone to treat CINV, as described in the claims, because Reddy et al. teaches aprepitant (an NK-1 antagonist) in combination with a 5-HT3 antagonist as the "standard of care for highly emetogenic chemotherapy," identifies netupitant as an alternative NK1 antagonist under clinical development, and further identifies palonosetron as an alternative 5-HT3 antagonist. With regard to the doses recited in the claims, the Office action states that it would have been obvious to optimize when and how much dexamethasone, netupitant and palonosetron is administered because they are taught to be useful for treating CINV.

Importantly, Reddy did not distinguish between vomiting and nausea as separate therapeutic targets, and instead lumped them together as one indication commonly referred to as

CINV. This is important because the term "CINV" is a misnomer. Even though CINV stands for chemotherapy induced nausea and vomiting, a compound that treats CINV is not necessarily able to treat both nausea and vomiting. As explained in the 132 Declaration of Giorgia Rossi and Claudio Pietra filed concurrently herewith, in paragraph 39,

> While the [CINV] indication states nausea, and this same terminology is used throughout the medical community, drug sponsors do not need to demonstrate an effect on nausea to secure approval for this indication. Rather, they are only required to demonstrate an effect on "complete response," defined as no emetic episodes (i.e. vomiting or retching) and no use of rescue therapy during the relevant time period.

This distinction is significant because nausea from chemotherapy has historically been much more difficult to treat than vomiting, even with NK1 antagonists. As explained by Ruhlmann et al., "These drugs [5-HT3 and NK_1 antiemetics] have had a huge impact in the protection from chemotherapy-induced vomiting, whereas the effect on nausea seems to be limited." Ruhlmann et al., "Casopitant: a novel NK_1-receptor antagonist in the prevention of chemotherapy-induced nausea and vomiting," in *Therapeutics and Clinical Risk Management* 5:375-384 (2009) (October 2012 IDS Ref. 2).

This point is best illustrated by FDA's approval of aprepitant (a/k/a Emend®), which is the only NK1 antagonist currently approved by FDA. (See FDA-approved Aprepitant Labeling in October 2012 IDS Ref. 1). As seen in the indications section of aprepitant's labeling, the drug is indicated for:

- in combination with other antiemetic agents for the:
  - prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including high-dose cisplatin (1.1)
  - prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC) (1.1)

However, in clinical trials of the drug, the sponsor (Merck) was not able to demonstrate a reduction in nausea or significant nausea. The following data is extracted from Tables 6 and 7 of aprepitant's labeling:

No Nausea			
Overall	48	44	NS**
Delayed phase	51	48	NS**
No Significant Nausea			
Overall	73	66	NS**
Delayed phase	75	69	NS**

No Nausea			
Overall	49	39	NS*
Delayed phase	53	40	NS*
No Significant Nausea			
Overall	71	64	NS**
Delayed phase	73	65	NS**

As can be seen, the drug did not achieve a statistically significant reduction in either nausea or significant nausea, in the overall period following chemotherapy (0-120 hrs) or the delayed phase following chemotherapy (25-120 hrs).

The claimed regimen differs from the aprepitant regimen described by Reddy because the claimed regimen treats both nausea and vomiting.

A. It would not have been obvious to combine netupitant and palonosetron for the treatment of nausea because there was no expectation of success.

As the Examiner is well aware, an invention would not have been obvious if the worker of ordinary skill would not have reasonably expected the invention to work. As stated in MPEP section 2143.02, a "reasonable expectation if success is required" for an invention to be obvious. In this case, a worker of ordinary skill would not have expected netupitant to successfully treat nausea because aprepitant – the only other NK1 antagonist approved for CINV, and the NK1 antagonist that allegedly supports the Examiner's prima facie case of obviousness – was unable to demonstrate a statistically significant effect on nausea in its clinical trials. This is probably what led Ruhlmann et al. to state that "the effect on nausea from NK1 antagonists seems to be limited."

The following table is taken from the 132 Declaration of Giorgia Rossi and Claudio Pietra filed concurrently herewith:

TABLE 2

	1	2	3	4	5	6	7	8
Efficacy Endpoint	Palo + Netu (HEC)[a]	Ondan + Aprep (HEC)[a]	Palo + Netu (MEC)[b]	Ondan + Aprep (MEC)[c]	Palo + Aprep (HEC)[d]	Palo + Aprep (MEC)[e]	Ondan + Aprep (MEC)[f]	Palo + Aprep (HEC)[g]
No Nausea								
Overall (0-120h)	61.5	58.2	50.3	ns	ns	32[nsc]	30.6[ns]	59.9[ncs]
Acute (0-24h)	80.0	77.6	ns	ns	ns			
Delayed (25-120h)	68.1*	60.4	ns	ns	ns			
No Significant Nausea								
Overall (0-120h)	89.6*	85.8	74.6*	ns	ns	56[ncs]	66.1[ns]	91[ncs]
Acute (0-24h)	98.5*	94.0	ns	ns	ns			
Delayed (25-120h)	90.4*	88.1	ns	ns	ns			

As can be seen, there are at least four controlled trials of aprepitant in the medical literature (columns 2, 4, 5 and 7), and in none of these trials was aprepitant able to demonstrate a statistically significant effect against nausea or significant nausea. This was true throughout the acute and delayed phases of emesis, it was true regardless of whether moderately emetogenic chemotherapy (MEC) or highly emetogenic chemotherapy (HEC) was administered. It was also true regardless of the 5-HT3 antagonist combined with aprepitant (i.e. ondansetron or palonosetron). Given this negative data for aprepitant, including data combining aprepitant with palonosetron, a worker of ordinary skill plainly would not have had a reasonable expectation of successfully treating nausea from the combination of netupitant and palonosetron.

However, that is exactly what the inventors have shown. As can be seen from columns 1 and 3, the combination of netupitant and palonosetron consistently reduced significant nausea in response to HEC, reduced nausea during the delayed phase in response to HEC, and reduced significant nausea during the overall phase in response to MEC. These results were unexpected, and they plainly support the patentability of the claimed invention. Compare MPEP 716.02 (Greater than expected results are evidence of nonobviousness).

In fact, Applicant questions whether Reddy even supports a prima facie case of obviousness. Under MPEP 2144.06, an examiner is allowed to substitute one drug for another when making a prima facie case of obviousness, but only if the two drugs are "art recognized equivalents for the same purpose." That rationale does not apply here because aprepitant and netupitant are not art recognized equivalents for the treatment of nausea.

Because a worker of ordinary skill would not have reasonably expected the combination of netupitant and palonosetron to treat nausea, the claimed invention would not have been obvious.

B. The references do not support a routine optimization rejection for the doses of netupitant, palonosetron and dexamethasone recited in the claims.

The Office asserts that once the decision to combine netupitant, palonosetron and dexamethasone was made, a worker of ordinary skill would have arrived at the doses recited in the claims, and the timing of such doses, through routine optimization. This assertion grossly over-simplifies the process of drug development, extends the doctrine of routine optimization further than it has ever been extended, and is not supported on the record at hand.

The doctrine of routine optimization presupposes a range of conditions in the prior art to be optimized, and that methods in the prior art exist for optimizing those conditions to arrive at the claimed invention. *In re Boesch,* 617 F.2d 272, 276 (CCPA 1980) ("it is generally considered the have been prima facie obvious to one of ordinary skill in the art to vary disclosed parameters to some extent for purposes of optimization.") The Reddy article cited by the Office does not support a routine optimization rejection because it does not include any prior art dosing ranges of netupitant, palonosetron and dexamethasone to be optimized, or methods for optimizing those ranges to arrive at the claimed invention.

With respect to netupitant, it is important to note that the dose of netupitant described in the claims is much higher than taught, for example, in U.S. Pat. No. 6,297,395 (teaching 5 mg per tablet, 10 mg per capsule and 15 mg per suppository in Examples A, B, and C at col. 83-84), U.S. Pat. No. 6,593,472 (same), and U.S. Pat. No. 6,719,996 (70 mg netupitant tablets taught in Examples 1-5 and Table 1 at col. 5-6). The prior art of record does not provide any rationale or

describe any methods for going from these relatively low doses of netupitant to the doses recited in the claims.

In addition, the worker of ordinary skill would have had no reason to conduct the optimization suggested by the rejection because, as stated in MPEP 2144.05, "only result-effective variables can be optimized." "A particular parameter must first be recognized as a result-effective variable, i.e., a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation." MPEP 2144.05. The claims in this case are directed at the treatment of nausea. However, it was not even known that the dose of netupitant could be modified to optimize the treatment of nausea before the inventors made this discovery. It was not even known that netupitant would treat nausea before the invention. The dose of netupitant was not a "result effective variable" for the treatment of nausea, and it is not a suitable object for the "routine optimization" rejection made by the Examiner.

The Examiner's "routine optimization" rejection also extends this doctrine well beyond its original roots. The doctrine was first established in In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955), for situations where the process of optimization was simple and routine. As explained in MPEP 2144.05, that case involved claims to a chemical reaction performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70%; the claims were held prima facie obvious over a prior art process which differed from the claims only in that the prior art process was performed at a temperature of 100°C and an acid concentration of 10%. Because there was such a small difference between the prior art reaction conditions and the reaction conditions recited in the claims, and because a single bench chemist working in a small laboratory could have optimized those conditions in just a few days to arrive at the claimed invention, the CCPA held that the claimed invention was the result of routine optimization and obvious.

Arriving at a dose and dosing regimen for netupitant and palonosetron that would effectively and safely treat nausea is a completely different story. There is no bench-test for evaluating the ability of a compound to treat nausea, and the Examiner has not cited any. There is not even an animal model for evaluating nausea. There are animal models that can be used to

evaluate reductions in vomiting and retching, but those models do not evaluate nausea because nausea must be communicated from the patient to the evaluator.

The only way to determine whether a molecule is able to treat nausea is to study the molecule in humans, in a well-controlled clinical trial, but that process is far from routine, and it requires studying hundreds of human patients to determine the optimum dose. The Board of Appeals has never held that the conduct of human clinical trials is "routine," or that conducting dose ranging trials in humans qualifies as routine optimization. It is certainly much more complicated and time consuming than the bench chemistry involved in In re Aller.

Finally, the Examiner has not cited any rationale for arriving at the dose of dexamethasone recited in claim 1, which is less than the effective amount of dexamethasone required to treat CINV when dexamethasone is administered alone. This dose is listed as 12 mg on day one in claim 14. Once again, the cited references do not support a routine optimization rejection because they do not give any rationale for going from a therapeutic dose of dexamethasone (16-20 mg) to a sub-therapeutic dose, or provide any methodology for arriving at this lower dose.

In conclusion, there was nothing "routine" about going from Reddy's regimen of aprepitant and a 5HT3 antagonist to the particular doses of netupitant, palonosetron and dexamethasone recited in the claims. The Examiner's "routine optimization" rejection is not supported by the record.

C. Netupitant and palonosetron exhibit synergy when combined.

Finally, Applicant wishes to point out the synergy it has observed between netupitant and palonosetron when they are combined to inhibit substance P activity in vitro. As stated in the 132 Declaration filed herewith, "This synergistic inhibition of substance-P response is an important discovery given the role substance-P plays in emetic pathways implicated in CINV, PONV, and radiotherapy induced nausea and vomiting ("RINV")."

The following statements from the 132 Declaration of Drs. Rossi and Pietra summarize Applicant's evidence of synergy, and the unexpected nature of this synergy. These statements show (1) that palonosetron is able to inhibit substance P activity when other 5-HT3 antagonists

are not, and (2) that palonosetron exhibits synergy when combined with netupitant to inhibit substance P activity.

12. Our discoveries in this area began with research into the potential impact of palonosetron individually on substance-P induced cellular signaling. Because substance-P is the natural ligand for the NK-1 receptor, and palonosetron is a ligand for the 5-HT3 receptor, we did not expect palonosetron to have any effect on substance-P response. However, we unexpectedly discovered that palonosetron inhibited the substance-P response. Even more surprisingly, we discovered that other established 5-HT3 antagonists, specifically ondansetron and granisetron, did not inhibit substance-P response.

13. The following Figure 1, taken from Stathis et al. (2012) (ref. B), illustrates this point:

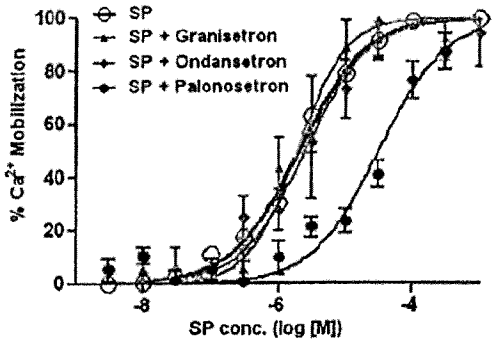


FIGURE 1

14. As can be seen, granisetron and ondansetron, which are both well-established 5-HT3 receptor antagonists, had no effect on substance-P induced Ca2+ mobilization in NG108-15 neuroblastoma cells. However, when palonosetron was added to the culture medium, the concentration of substance-P required to induce Ca2+ mobilization (the "EC50") was nearly an order of magnitude higher.

15. We next tested the combined effect of palonosetron and netupitant against substance-P. In these experiments, the two molecules exhibited synergy when combined.

16. We first exposed NG108-15 neuroblastoma cells to netupitant and palonosetron at various concentrations for 1 hour at 37 °C. After the netupitant and palonosetron were removed from the cell culture, the culture medium was incubated with substance-P at various concentrations

(3 nM to 1mM) for 1 hour at 37 °C, followed by measurement of Ca2+ mobilization.

17. The EC50 of substance-P in these experiments is reported below in Table 1.

TABLE 1

Inhibition of SP response in NG108-15 cells by netupitant (netu) and palonosetron (palo).

SP + Antagonist(s)	EC_{50} (μM) ± S.E.M.	*n*
SP only	2 ± 0.2	38
Plus netu (1 nM)	2 ± 0.3	3
Plus netu (3 nM)	5 ± 3	3
Plus netu (10 nM)	10 ± 0.9	3
Plus netu (30 nM)	40 ± 10[a]	6
Plus palo (0.2 nM)	2 ± 0.1	3
Plus palo (0.6 nM)	3 ± 0.6	3
Plus palo (2 nM)	10 ± 2	3
Plus palo (6 nM)	30 ± 6[a]	5
Plus net (1 nM) plus palo (0.2 nM)	120 ± 20[b]	7
Plus net (30 nM) plus palo (6 nM)	970 ± 150[c]	5

18. As can be seen, netupitant at 1 nM did not exhibit any effect on substance-P response, as measured by EC50. However, as the concentrations of netupitant rose to 3, 10 and 30 nM, we observed corresponding increases in the effect on substance-P response, with maximal inhibition observed at 30 nM netupitant.

19. In like manner, palonosetron exhibited a threshold concentration of 0.2 nM at which there was no effect on substance-P response. However, as the concentration of palonosetron rose to 0.6, 2, and 6 nM, we observed corresponding increases in substance-P inhibition, and maximal inhibition at 6 nM.

20. We then combined palonosetron and netupitant in the same experiment to determine their combined effect on substance-P response. Our first experiment was with netupitant (1 nM) plus palonosetron (0.2 nM) – the highest concentrations we had tested where neither had inhibited substance-P response individually.

21. As can be seen, this combination displayed a startling level of synergy in these experiments. At concentrations where neither individual molecule increased the EC50 of substance P, the combination of molecules increased the EC50 of substance-P from 2 uM to 120 uM, a sixty-fold increase in the EC50 of substance-P. The additive increase should have been zero.

> 22. Synergy was also observed at the other concentrations of netupitant and palonosetron tested. As seen from Table 1, 30 nM netupitant by itself increased the EC50 of substance-P by 38 uM, from 2 uM to 40 uM. 6 nM palonosetron by itself increased the EC50 of substance-P by 28 uM, from 2 uM to 30 uM.
>
> 23. The additive effect of the two ingredients might thus be expected to be 66 uM (38uM for netupitant + 28 uM for palonosetron). However, when we tested the combination, we observed an increase in EC50 to 970 uM, nearly 500-fold.
>
> 24. These results clearly demonstrate the synergy between palonosetron and netupitant on the substance-P pathway, and their beneficial activity in emetic conditions mediated by substance-P, including CINV, PONV and RINV.

The International Preliminary Report on Patentability issued in the PCT counterpart of this application had this to say about synergy:

> Therefore, unless combining these compounds gives rise to an unexpected technical effect, such as synergy, or overcomes a technical prejudice, no inventive effort is needed to arrive at the solution of providing this combination as a solution to the problem of finding a treatment of nausea and vomiting.

The MPEP at section 716.02(d) makes similar observations about synergy:

> A greater than expected result is an evidentiary factor pertinent to the legal conclusion of obviousness ... of the claims at issue." *In re Corkill*, 711 F.2d 1496, 226 USPQ 1005 (Fed. Cir. 1985). ... Evidence of a greater than expected result may also be shown by demonstrating an effect which is greater than the sum of each of the effects taken separately (i.e., demonstrating "synergism"). Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989). However, a greater than additive effect is not necessarily sufficient to overcome a prima facie case of obviousness because such an effect can either be expected or unexpected. Applicants must further show that the results were greater than those which would have been expected from the prior art to an unobvious extent, and that the results are of a significant, practical advantage.

The synergy data in the enclosed 132 Declaration of Giorgia Rossi and Claudio Pietra satisfy both of the foregoing requirements. The combination "demonstrates an effect which is

greater than the sum of each of the effects taken separately." In addition, the greater than additive effect could not have been expected from the prior art, because molecules other than palonosetron had no effect against substance-P whatsoever.

This evidence of synergy rebuts any prima facie case of obviousness the Examiner has stated, and proves the nonobviousness of the claimed invention.

CONCLUSION

This reply is believed to provide a full and complete response. In light of the above remarks, the Applicant requests that the Patent Office consider this application with a view toward allowance. Should the Examiner have any questions or concerns regarding this application, he is invited to contact the undersigned at 404-873-8512.

To the extent any fees are due for this submission, or any further extension of time is required, the Commissioner is authorized to charge deposit account number 504667.

Respectfully submitted,

ARNALL GOLDEN GREGORY LLP

/Clark G. Sullivan/
Clark G. Sullivan
Registration No. 36,942

May 17, 2013

ARNALL GOLDEN GREGORY LLP
(404) 873-8500
(404) 873-8501 (fax)
Customer No.: 53449

Attorney Docket No.: 23278.20.US.2

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application:	)	
	)	
Fabio TRENTO *et al.*	)	Examiner: Walter E. Webb
	)	
Serial No.: 13/077,462	)	Art Unit: 1612
	)	
Filed: March 31, 2011	)	Confirmation No.: 5608
	)	
For: Compositions and Methods for Treating Centrally Mediated Nausea and Vomiting	)	

REQUEST FOR EXTENSION OF TIME

Commissioner of Patents
United States Patent Office
Alexandria, Virginia

ARNALL GOLDEN GREGORY
Customer Number 53449

Dear Sir:

It is respectfully requested that an extension of time for the period indicated below be granted in accordance with the provisions of 37 C.F.R. Section 1.136 to take action required in the application identified in the caption, as reflected by the papers submitted herewith:

☐	One Month	$200.00	($100.00)*
☐	Two Months	$600.00	($300.00)*
☒	Three Months	$1,400.00	($700.00)*
☐	Four Months	$2,200.00	($1,100.00)*
☐	Five Months	$3,000.00	($1,500.00)*

* Small Entity

A credit card payment is being made electronically in the amount of $700.00 for the fee for a small entity under 37 C.F.R. § 1.17(a)(2). This amount is believed to be correct; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment, to Deposit Account No. 50-4667.

Respectfully submitted,

ARNALL GOLDEN GREGORY LLP

/Clark G. Sullivan/
Clark G. Sullivan
Registration No. 36,942

May 17, 2013

ARNALL GOLDEN GREGORY LLP
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application:	)	
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Filed: March 31, 2011	)	Confirmation No.: 5608
	)	
For: Compositions and Methods for Treating Centrally Mediated Nausea and Vomiting	)	

COMBINED DECLARATION OF GIORGIA ROSSI AND CLAUDIO PIETRA
37 C.F.R. § 1.132

1. Our names are Giorgia Rossi and Claudio Pietra.
2. We are each of the age of majority and qualified to give testimony to the matters discussed herein.
3. We are each employees of Helsinn Healthcare SA, the assignee of the above-referenced application.
4. For convenience, we will refer to ourselves herein using the third person.
5. Giorgia Rossi is a Medical Doctor with a degree in medicine from the University of Milan. She is an inventor for this application and has been actively involved in the clinical development of a combination drug product containing netupitant and palonosetron since arriving at Helsinn Healthcare in 2005. Giorgia Rossi's contribution to this declaration, to the exclusion of Claudio Pietra, is in paragraphs 28 through 36
6. Claudio Pietra is the Director of pre-clinical studies at Helsinn Healthcare responsible for all investigations relating to Helsinn's drugs other than human clinical trials. He has a Master's Degree in Chemistry and Pharmaceutical Techniques from the University of Pavia, and has been responsible for all non-human investigations of palonosetron and netupitant since arriving

at Helsinn Healthcare in 2005. Claudio Pietra's particular contribution to this declaration, to the exclusion of Giorgia Rossi, is in paragraphs 10 through 24.

7. Palonosetron is a synthetic antagonist of the 5-hydroxytryptamine (5-HT3) receptor, first described in U.S. Patent No. 5,202,303. It is approved for the treatment of chemotherapy induced nausea and vomiting ("CINV") resulting from moderately-emetogenic and highly-emetogenic chemotherapy, as well as post-operative nausea and vomiting ("PONV").
8. Netupitant is a synthetic antagonist of the neurokinin-1 receptor (NK-1), first described in U.S. Patent No. 6,297,375. Netupitant is not currently approved by FDA. However, Helsinn has recently completed investigating a combination of netupitant with palonosetron in phase III clinical trials for the treatment of CINV.
9. We have performed or overseen numerous experiments and studies involving the combination of netupitant and palonosetron during Helsinn's development of this drug, and report some of our investigations herein.
10. One of the most surprising aspects of our research is the synergy observed when netupitant and palonosetron are combined to inhibit substance-P response.
11. This synergistic inhibition of substance-P response is an important discovery given the role substance-P plays in emetic pathways implicated in CINV, PONV, and radiotherapy induced nausea and vomiting ("RINV"). See Reddy *et al.* (2006) (ref. A) (reporting complementary roles of 5-HT3 and NK-1 signaling pathways in pathogenesis of emetic response).
12. Our discoveries in this area began with research into the potential impact of palonosetron individually on substance-P induced cellular signaling. Because substance-P is the natural ligand for the NK-1 receptor, and palonosetron is a ligand for the 5-HT3 receptor, we did not expect palonosetron to have any effect on substance-P response. However, we unexpectedly discovered that palonosetron inhibited the substance-P response. Even more surprisingly, we discovered that other established 5-HT3 antagonists, specifically ondansetron and granisetron, did not inhibit substance-P response.
13. The following Figure 1, taken from Stathis *et al.* (2012) (ref. B), illustrates this point:

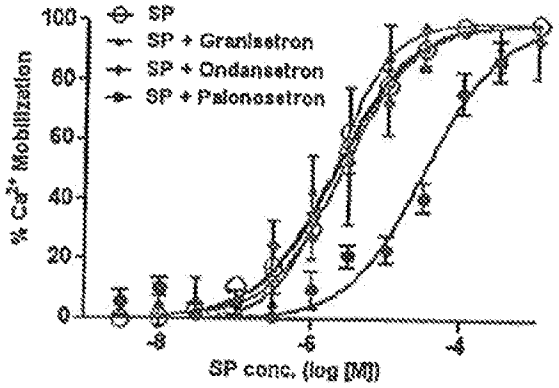


FIGURE 1

14. As can be seen, granisetron and ondansetron, which are both well-established 5-HT3 receptor antagonists, had no effect on substance-P induced Ca^{2+} mobilization in NG108-15 neuroblastoma cells. However, when palonosetron was added to the culture medium, the concentration of substance-P required to induce Ca^{2+} mobilization (the "EC_{50}") was nearly an order of magnitude higher.

15. We next tested the combined effect of palonosetron and netupitant against substance-P. In these experiments, the two molecules exhibited synergy when combined.

16. We first exposed NG108-15 neuroblastoma cells to netupitant and palonosetron at various concentrations for 1 hour at 37 °C. After the netupitant and palonosetron were removed from the cell culture, the culture medium was incubated with substance-P at various concentrations (3 nM to 1mM) for 1 hour at 37 °C, followed by measurement of Ca^{2+} mobilization.

17. The EC_{50} of substance-P in these experiments is reported below in Table 1.

TABLE 1

Inhibition of SP response in NG108-15 cells by netupitant (netu) and palonosetron (palo).

SP + Antagonist(s)	EC_{50} (μM) ± S.E.M.	n
SP only	2 ± 0.2	38
Plus netu (1 nM)	2 ± 0.3	3
Plus netu (3 nM)	5 ± 3	3
Plus netu (10 nM)	10 ± 0.9	3
Plus netu (30 nM)	40 ± 10[a]	6
Plus palo (0.2 nM)	2 ± 0.1	3
Plus palo (0.6 nM)	3 ± 0.6	3
Plus palo (2 nM)	10 ± 2	3
Plus palo (6 nM)	30 ± 6[a]	5
Plus net (1 nM) plus palo (0.2 nM)	120 ± 20[b]	7
Plus net (30 nM) plus palo (6 nM)	970 ± 150[c]	5

18. As can be seen, netupitant at 1 nM did not exhibit any effect on substance-P response, as measured by EC_{50}. However, as the concentrations of netupitant rose to 3, 10 and 30 nM, we observed corresponding increases in the effect on substance-P response, with maximal inhibition observed at 30 nM netupitant.
19. In like manner, palonosetron exhibited a threshold concentration of 0.2 nM at which there was no effect on substance-P response. However, as the concentration of palonosetron rose to 0.6, 2, and 6 nM, we observed corresponding increases in substance-P inhibition, and maximal inhibition at 6 nM.
20. We then combined palonosetron and netupitant in the same experiment to determine their combined effect on substance-P response. Our first experiment was with netupitant (1 nM) plus palonosetron (0.2 nM) – the highest concentrations we had tested where neither had inhibited substance-P response individually.
21. As can be seen, this combination displayed a startling level of synergy in these experiments. At concentrations where neither individual molecule increased the EC_{50} of substance P, the combination of molecules increased the EC_{50} of substance-P from 2 uM to 120 uM, a sixty-fold increase in the EC_{50} of substance-P. The additive increase should have been zero.
22. Synergy was also observed at the other concentrations of netupitant and palonosetron tested. As seen from Table 1, 30 nM netupitant by itself increased the EC_{50} of substance-P by 38 uM, from 2 uM to 40 uM. 6 nM palonosetron by itself increased the EC50 of substance-P by 28 uM, from 2 uM to 30 uM.
23. The additive effect of the two ingredients might thus be expected to be 66 uM (38uM for netupitant + 28 uM for palonosetron). However, when we tested the combination, we observed an increase in EC_{50} to 970 uM, nearly 500-fold.
24. These results clearly demonstrate the synergy between palonosetron and netupitant on the substance-P pathway, and their beneficial activity in emetic conditions mediated by substance-P, including CINV, PONV and RINV.
25. We understand that the Examiner contends that it would have been obvious to combine netupitant with palonosetron for the treatment of chemotherapy-induced nausea and vomiting based on Reddy *et al.* (2006) (ref. A).

26. In particular, we understand that the Examiner contends that Reddy *et al.* (2006) (ref. A) describes the combination of aprepitant and a 5-HT3 antagonist for the treatment of CINV, as well as casopitant and a 5-HT3 antagonist for the treatment of CINV, and that it would have been obvious to use netupitant and palonosetron in these treatments because netupitant, aprepitant, and casopitant are all NK-1 antagonists, and palonosetron is a 5-HT3 antagonist.
27. However, GlaxoSmithKline has discontinued its development of casopitant due to toxicity issues (see Press Release ref. C).
28. In addition, we have generated unexpectedly superior results when using netupitant against CINV instead of aprepitant. In particular, we have observed an unanticipated statistically significant effect against nausea from the combination of netupitant and palonosetron that has not previously been observed in clinical studies involving the combination of aprepitant with ondansetron or aprepitant with palonosetron.
29. As seen below in Table 2 columns 1 and 3, the combination of netupitant with palonosetron produced statistically significant relief against nausea in Helsinn's clinical trials, protecting patients from nausea whether they received highly emetogenic chemotherapy ("HEC") or moderately emetogenic chemotherapy ("MEC").
30. The combination was especially effective at protecting patients from significant nausea in response to HEC. As can be seen in column 1, the combination of netupitant with palonosetron, when compared to palonosetron alone, produced statistically significant relief against significant nausea during the acute phase of HEC-induced CINV, the delayed phase of HEC-induced CINV, and the overall phase of HEC-induced CINV.
31. When compared to palonosetron alone, the combination of netupitant with palonosetron also produced statistically significant relief against nausea in the delayed phase of HEC (column 1), and against significant nausea in the overall phase of MEC (column 3).
32. In contrast, as can be seen from columns 2, 4, 4a and 7, in five separate controlled clinical trials the combination of aprepitant and ondansetron did not produce significant relief against nausea or significant nausea in response to HEC or MEC. In the HEC study reported in column 2, no significant benefit was observed against nausea or significant nausea in the overall phase (0-120 h), the acute phase (0-24 h), or the delayed phase (25-120 h). The HEC studies described in column 4a only reported data for the overall phase (0-120 h) and the delayed phase (25-120

h), and no statistically significant benefit against nausea or significant nausea was observed in either phase. The MEC studies described in columns 4 and 7 only reported data for the overall phase (1-120 h), and no statistically significant benefit was observed in this phase.

TABLE 2

	1	2	3	4	4a	5	6	7	8
Efficacy Endpoint	Palo + Netu (HEC)[a]	Ondan + Aprep (HEC)[a]	Palo + Netu (MEC)[b]	Ondan + Aprep (MEC)[c]	Ondan + Aprep (HEC)[c1]	Palo + Aprep (HEC)[d]	Palo + Aprep (MEC)[e]	Ondan + Aprep (MEC)[f]	Palo + Aprep (HEC)[g]
Percentage of Patients with No Nausea									
Overall (0-120h)	61.5	58.2	50.3	33	48,49	nr	32[ncs]	30.6	59.9[ncs]
Acute (0-24h)	80.0	77.6	70.4	nr	nr,nr	nr	nr	nr	nr
Delayed (25-120h)	68.1*	60.4	53.3	nr	51,53	nr	nr	nr	nr
Percentage of Patients with No Significant Nausea									
Overall (0-120h)	89.6*	85.8	74.6*	61	73,71	88.5	56[ncs]	66.1	91[ncs]
Acute (0-24h)	98.5*	94.0	87.3	nr	nr,nr	nr	nr	nr	nr
Delayed (25-120h)	90.4*	88.1	76.9	nr	75,73	nr	nr	nr	nr

*Statistically Significant ($p < 0.05$)
[nr] Data Not Reported
[ncs] Non-Comparative Study; statistical significance not evaluated
[a] Helsinn Study NETU-07-07
[b] Helsinn Study NETU-08-18
[c] Warr *et al.* (2005) (Ref. D)
[c1] FDA-Approved Prescribing Information for Emend® (aprepitant) (results of two studies reported) (Ref. E)
[d] Herrington *et al.* (2008) (Ref. F)
[e] Grunberg *et al.* (2008) (Ref. G)
[f] Yeo *et al.* (2009) (Ref. H)
[g] Longo *et al.* (2012) (Ref. I)

33. Table 2 also includes data from three clinical trials of aprepitant combined with palonosetron in columns 5, 6 and 8.

34. As can be seen, the combination of aprepitant with palonosetron was not able to produce a statistically significant reduction in nausea or significant nausea in the HEC study reported in column 5, while the combination of netupitant with palonosetron reported in column 1 was.

35. In addition, the combination of netupitant with palonosetron was able to protect a much higher proportion of patients against nausea than the combination of aprepitant with palonosetron when tested in MEC. A comparison of columns 3 and 6 shows that the combination of netupitant and palonosetron was able to protect 50% of the patients from nausea while the combination of aprepitant with palonosetron only protected 32% of the patients.
36. A comparison of columns 3 and 6 reveals a similar difference when evaluating significant nausea. The combination of netupitant with palonosetron protected 75% of the MEC patients from significant nausea while the combination of aprepitant with palonosetron only protected 56% of the patients.
37. All of these facts support the unique efficacy from the combination of palonosetron with netupitant that is not seen in prior art aprepitant regimens. This efficacy could not have been predicted from prior studies of other NK1/5-HT3 combinations. In fact, the data in Table 2 is consistent with the synergy data we observed *in vitro* from this combination.
38. Finally, it is important here to clarify the approval requirements for an FDA-approved indication of "prevention of chemotherapy induced *nausea* and vomiting." While the indication states nausea, and this same terminology is used throughout the medical community, drug sponsors do not need to demonstrate an effect on nausea to secure approval for this indication. Rather, they are only required to demonstrate an effect on "complete response," defined as no emetic episodes (i.e. vomiting or retching) and no use of rescue therapy during the relevant time period.

[SIGNATURES ON FOLLOWING PAGE]

We hereby declare under penalty of perjury, pursuant to 28 U.S.C. § 1746, that the foregoing is true and correct to the best of our knowledge, information, and belief.

Date: 16-May-2013 Date: .....

Giorgia Rossi

Giorgia Rossi Claudio Pietra

5463395v3

We hereby declare under penalty of perjury, pursuant to 28 U.S.C. § 1746, that the foregoing is true and correct to the best of our knowledge, information, and belief.

Date: _____

Giorgia Rossi

Date: May 14th 2013

Claudio Pietra

BIBLIOGRAPHY

A. Reddy *et al.*, Novel neurokinin-1 antagonists as antiemetics for the treatment of chemotherapy-induced emesis. (2006) Support Cancer Ther. 3(3):140-2.

B. Stathis *et al.*, Inhibition of substance P-mediated responses in NG108-15 cells by netupitant and palonosetron exhibit synergistic effects. (2012) Eur. J. Pharm. 689:25-30.

C. Press Release, GSK provides update on regulatory filings for Zunrisa/Rezonic; Issued: Monday 28 September 2009, London UK.

D. 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.

E. Emend® FDA Approved Labeling (March 27, 2003)

F. 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.

G. Grunberg *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. (2008) Support Care Cancer (online publication).

H. 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.

I. 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.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application:	)	
	)	
Fabio TRENTO *et al.*	)	Examiner: Walter E. Webb
	)	
Serial No.: 13/077,462	)	Art Unit: 1612
	)	
Filed: March 31, 2011	)	Confirmation No.: 5608
	)	
For: Compositions and Methods for Treating Centrally Mediated Nausea and Vomiting	)	

INFORMATION DISCLOSURE STATEMENT

Commissioner of Patents
United States Patent Office
Alexandria, Virginia

ARNALL GOLDEN GREGORY
Customer Number 53449

Dear Sir:

Pursuant to the requirements of 37 C.F.R. § 1.56, submitted herewith on the accompanying Information Disclosure Statement List is a listing of documents known to Applicants and/or their attorneys. In accordance with 37 C.F.R. § 1.98(a)(2), copies of any cited U.S. patent or U.S. patent application publication documents are not enclosed. Copies of any cited foreign patent document and/or any non-patent publication are enclosed.

In accordance with 37 C.F.R. § 1.97(d), Applicant includes herewith the payment specified in 37 C.F.R. § 1.17(p). Applicants believe that no further fees are due with this Information Disclosure Statement. However, the Commissioner is hereby authorized to charge any further fees which may be required, or credit any overpayment, to Deposit Account No. 50-4667.

Respectfully submitted,

ARNALL GOLDEN GREGORY LLP

/Clark G. Sullivan/
Clark G. Sullivan
Registration No. 36,942

May 17, 2013

ARNALL GOLDEN GREGORY LLP
(404) 873-8500
(404) 873-8501 (fax)
Customer No.: 53449

Attorney Docket No.: 23278.20.US.2

PTO/SB/08a (01-10)
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	13077462
Filing Date	2011-03-31
First Named Inventor	Fabio Trento
Art Unit	1615
Examiner Name	Walter E. Webb
Attorney Docket Number	23278.20.US.2

U.S.PATENTS

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
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	1							☐

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NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, 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	13077462
	Filing Date	2011-03-31
	First Named Inventor	Fabio Trento
	Art Unit	1615
	Examiner Name	Walter E. Webb
	Attorney Docket Number	23278.20.US.2

	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)	☐

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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	13077462
	Filing Date	2011-03-31
	First Named Inventor	Fabio Trento
	Art Unit	1615
	Examiner Name	Walter E. Webb
	Attorney Docket Number	23278.20.US.2

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)	2013-05-17
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.**

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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.

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Electronic Patent Application Fee Transmittal

Application Number:	13077462
Filing Date:	31-Mar-2011
Title of Invention:	Compositions and Methods for Treating Centrally Mediated Nausea and Vomiting
First Named Inventor/Applicant Name:	Fabio Trento
Filer:	Clark G. Sullivan/Susan Wray
Attorney Docket Number:	23278.20 (US2)

Filed as Small Entity

Utility under 35 USC 111(a) Filing Fees

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:				
Extension - 3 months with $0 paid	2253	1	700	700

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	2806	1	90	90
		Total in USD ($)		**790**

Electronic Acknowledgement Receipt

EFS ID:	15808105
Application Number:	13077462
International Application Number:	
Confirmation Number:	5608
Title of Invention:	Compositions and Methods for Treating Centrally Mediated Nausea and Vomiting
First Named Inventor/Applicant Name:	Fabio Trento
Customer Number:	53449
Filer:	Clark G. Sullivan/Susan Wray
Filer Authorized By:	Clark G. Sullivan
Attorney Docket Number:	23278.20 (US2)
Receipt Date:	17-MAY-2013
Filing Date:	31-MAR-2011
Time Stamp:	15:59:17
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
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Payment was successfully received in RAM	$790
RAM confirmation Number	2854
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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

1	Amendment/Req. Reconsideration-After Non-Final Reject	23278_20_US_2_AMENDMENT_AND_RESPONSE_TO_OFFICE_ACTION.pdf	1975230 59f6704c2af3f453f808be455bcbb13630ceb278	no	19
Warnings:					
Information:					
2	Extension of Time	23278_20_US_2_REQUEST_FOR_EXTENSION_OF_TIME.pdf	97622 8d17d3fb6b51843a9fd1c63a716a90dad8f5d1f8	no	2
Warnings:					
Information:					
3	Affidavit-traversing rejectns or objectns rule 132	23278_20_US_2_COMBINED_132_DECLARATION_OF_ROSSI_AND_PIETRA_5540694.pdf	1852593 16c8311d8ff00e1d6a99c9f09f8f87f920fe5ec8	no	10
Warnings:					
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4	Transmittal Letter	23278_20_US_2_INFORMATION_DISCLOSURE_STATEMENT_TRANSMITTAL.pdf	97186 321ba5b1df3bbf5110f86087cf7b751060b5bcec	no	2
Warnings:					
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5	Information Disclosure Statement (IDS) Form (SB08)	23278_20_US_2_INFORMATION_DISCLOSURE_STATEMENT_SB08.pdf	584373 dd4bb5953c225f65080fd52e0d49674ef6b5669e	no	4
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7	Non Patent Literature	23278_20_US_2_NPL_CITE_2_WARR_EFFICACY_AND_TOLERABILITY_OF_APREPITANT.pdf	3578127 019dc22e58abba2cf1db84daf400e0f76939eeb2	no	10
Warnings:					
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8	Non Patent Literature	23278_20_US_2_NPL_CITE_3_HERRINGTON_RANDOMIZED_PLACEBO_CONTROLLED_PILOT_STUDY_5263129.pdf	154147 ad04933acc4b40c6a0bd37d34e855dfa0a5527af	no	8
Warnings:					
Information:					
9	Non Patent Literature	23278_20_US_2_NPL_CITE_4_YEO_A_RANDOMIZED_STUDY_5545708.pdf	1377357 d97dd3106748ff7b4b0fb7ce47e2f85d252dad2f	no	7

Warnings:					
Information:					
10	Non Patent Literature	23278_20_US_2_NPL_CITE_5_LONGO_PALONOSETRON_5545712.pdf	1405666 90d9972758cc0359be631418a92587a305ea3c8b	no	6
Warnings:					
Information:					
11	Non Patent Literature	23278_20_US_2_NPL_CITE_6_PRESS_RELEASE_NK1_RECEPTOR_ANTAGONIST_BY_ROCHE_5531574.pdf	1471038 a89343a43fdc0f4f500792565e0333fc291842f0	no	4
Warnings:					
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12	Fee Worksheet (SB06)	fee-info.pdf	32283 8b6c55aceb741c6dac3a924a32992c343963c5cb	no	2
Warnings:					
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			Total Files Size (in bytes):	12701229	

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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.

<u>National Stage of an International Application under 35 U.S.C. 371</u>
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.

<u>New International Application Filed with the USPTO as a Receiving Office</u>
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/06 (09-11)
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 13/077,462	Filing Date 03/31/2011	☐ 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 **05/17/2013**

	(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))	* 25	Minus	** 56	= 0	X $40 =	0
Independent (37 CFR 1.16(h))	* 5	Minus	***5	= 0	X $210 =	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.

LIE
/LAMONT MCLAUCHLIN/

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53449 7590 08/01/2013

PATENT CORRESPONDENCE
ARNALL GOLDEN GREGORY LLP
171 17TH STREET NW
SUITE 2100
ATLANTA, GA 30363

EXAMINER
WEBB, WALTER E

ART UNIT	PAPER NUMBER
1612	

DATE MAILED: 08/01/2013

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/077,462	03/31/2011	Fabio Trento	23278.20 (US2)	5608

TITLE OF INVENTION: Compositions and Methods for Treating Centrally Mediated Nausea and Vomiting

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$890	$300	$0	$1190	11/01/2013

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

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

HOW TO REPLY TO THIS NOTICE:

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

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

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

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

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

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

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

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

53449 7590 08/01/2013
PATENT CORRESPONDENCE
ARNALL GOLDEN GREGORY LLP
171 17TH STREET NW
SUITE 2100
ATLANTA, GA 30363

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

Certificate of Mailing or Transmission

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

(Depositor's name)
(Signature)
(Date)

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13/077,462	03/31/2011	Fabio Trento	23278.20 (US2)	5608

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nonprovisional	SMALL	$890	$300	$0	$1190	11/01/2013

EXAMINER	ART UNIT	CLASS-SUBCLASS
WEBB, WALTER E	1612	514-017700

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

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,

(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____

2 _____

3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:

❑ Issue Fee

❑ Publication Fee (No small entity discount permitted)

❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**

❑ A check is enclosed.

❑ Payment by credit card. Form PTO-2038 is attached.

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29	NOTE: Absent a valid certification of Micro Entity Status (see form PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
❑ Applicant asserting small entity status. See 37 CFR 1.27	NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
❑ Applicant changing to regular undiscounted fee status.	NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 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, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

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.
13/077,462	03/31/2011	Fabio Trento	23278.20 (US2)	5608

53449 7590 08/01/2013

PATENT CORRESPONDENCE
ARNALL GOLDEN GREGORY LLP
171 17TH STREET NW
SUITE 2100
ATLANTA, GA 30363

EXAMINER	
WEBB, WALTER E	
ART UNIT	PAPER NUMBER
1612	

DATE MAILED: 08/01/2013

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 34 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 34 day(s).

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

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.

Notice of Allowability	Application No. 13/077,462	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--

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

1. ☒ This communication is responsive to *Applicants response filed 5/17/2013*.
   ☒ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on *17 May,2013.*
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are *1-9,11-15,23-31,52 and 53*. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov .
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some *c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

   Interim copies:

   a) ☐ All b) ☐ Some c) ☐ None of the: Interim copies of the priority documents have been received.

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

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

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

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

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 5/17/2013
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
5. ☐ Examiner's Amendment/Comment
6. ☒ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/WALTER WEBB/
Primary Examiner, Art Unit 1612

REASONS FOR ALLOWANCE

The following is an examiner's statement of reasons for allowance: 132 Declaration, filed 5/17/2013, affiant showing evidence of synergy (unexpected result) from the combination of netupitant and palonosetron in regard to the claimed method.

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

Correspondence

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-4:00pm Mon-Fri 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

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13077462	TRENTO ET AL.
	Examiner	**Art Unit**
	WALTER WEBB	1612

CPC		
Symbol	**Type**	**Version**

CPC Combination Sets				
Symbol	**Type**	**Set**	**Ranking**	**Version**

US ORIGINAL CLASSIFICATION		INTERNATIONAL CLASSIFICATION														
CLASS	**SUBCLASS**	**CLAIMED**									**NON-CLAIMED**					
514	17.7	A	6	1	K	31 / 573 (2006.01.01)										
CROSS REFERENCE(S)		A	6	1	K	31 / 4178 (2006.01.01)										
		A	6	1	P	1 / 08 (2006.01.01)										
CLASS	**SUBCLASS (ONE SUBCLASS PER BLOCK)**	A	6	1	K	9 / 00 (2006.01.01)										
514	17.7 183 185 187 188	A	6	1	K	9 / 20 (2006.01.01)										
514	872	A	6	1	K	9 / 48 (2006.01.01)										

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 25
/WALTER WEBB/ Primary Examiner.Art Unit 1612 (Primary Examiner)	07/18/2013 (Date)	O.G. Print Claim(s) Claim 1 O.G. Print Figure None

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13077462	TRENTO ET AL.
	Examiner	**Art Unit**
	WALTER WEBB	1612

						A	6	1	K	31 / 496 (2006.01.01)						
						A	6	1	K	31 / 473 (2006.01.01)						

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 25	
/WALTER WEBB/ Primary Examiner.Art Unit 1612 (Primary Examiner)	07/18/2013 (Date)	O.G. Print Claim(s) Claim 1	O.G. Print Figure None

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13077462	TRENTO ET AL.
	Examiner	**Art Unit**
	WALTER WEBB	1612

☒ **Claims renumbered in the same order as presented by applicant** ☐ **CPA** ☐ **T.D.** ☐ **R.1.47**

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	1	17	25												
2	2	18	26												
3	3	19	27												
4	4	20	28												
5	5	21	29												
6	6	22	30												
7	7	23	31												
8	8	24	52												
9	9	25	53												
10	11														
11	12														
12	13														
13	14														
14	15														
15	23														
16	24														

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 25	
/WALTER WEBB/ Primary Examiner.Art Unit 1612 (Primary Examiner)	07/18/2013 (Date)	O.G. Print Claim(s) Claim 1	O.G. Print Figure None

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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. 5608

SERIAL NUMBER	FILING or 371(c) DATE RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
13/077,462	03/31/2011	424	1612	23278.20 (US2)

APPLICANTS

Fabio Trento, Pare (Como), ITALY;
Sergio Cantoreggi, Cagiallo, SWITZERLAND;
Giorgia Rossi, Cernobbio (Como), ITALY;
Roberta Cannella, Varese, ITALY;
Daniele Bonadeo, Casalzuigno, ITALY;

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

This appln claims benefit of 61/382,709 09/14/2010

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

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED **** ** SMALL ENTITY **
04/13/2011

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	51	5

ADDRESS

PATENT CORRESPONDENCE
ARNALL GOLDEN GREGORY LLP
171 17TH STREET NW
SUITE 2100
ATLANTA, GA 30363
UNITED STATES

TITLE

Compositions and Methods for Treating Centrally Mediated Nausea and Vomiting

FILING FEE RECEIVED		
1878	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 (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	219	palonosetron	USPAT; UPAD	OR	ON	2013/07/18 11:10
L2	45	aloxi	USPAT; UPAD	OR	ON	2013/07/18 11:10
L3	250	l1 or l2	USPAT; UPAD	OR	ON	2013/07/18 11:10
L4	6	netupitant	USPAT; UPAD	OR	ON	2013/07/18 11:11
L5	3	l4 and l3	USPAT; UPAD	OR	ON	2013/07/18 11:11
L6	18056	nausea or vomiting or emesis	USPAT; UPAD	OR	ON	2013/07/18 11:13
L7	125	l6 and l3	USPAT; UPAD	OR	ON	2013/07/18 11:13

7/ 18/ 2013 11:43:30 AM
C:\ Users\ wwebb\ Documents\ EAST\ Workspaces\ 13077462_netupitant dexamethasone palonosetron emesis nausea vomiting.wsp

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	13077462
Filing Date	2011-03-31
First Named Inventor	Fabio Trento
Art Unit	~~1615~~
Examiner Name	Walter E. Webb
Attorney Docket Number	23278.20.US.2

U.S.PATENTS

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.

U.S.PATENT APPLICATION PUBLICATIONS

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.

FOREIGN PATENT DOCUMENTS

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

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /W.W./

INFORMATION DISCLOSURE STATEMENT BY APPLICANT
(Not for submission under 37 CFR 1.99)

Application Number	13077462
Filing Date	2011-03-31
First Named Inventor	Fabio Trento
Art Unit	~~4645~~
Examiner Name	Walter E. Webb
Attorney Docket Number	23278.20.US.2

	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)	☐

If you wish to add additional non-patent literature document citation information please click the Add button

EXAMINER SIGNATURE

Examiner Signature	/Walter Webb/	Date Considered	07/18/2013

*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
	13077462	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	218	11/13/2012	WW

SEARCH NOTES		
Search Notes	Date	Examiner
Inventors Name Search on PALM	11/13/2012	WW
EAST Search History	11/13/2012	WW
NPL Search Terms: palonosetron, dexamethasone, netupinant, neurokinin-1, emesis, nausea, vomiting	11/13/2012	WW

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
514	352	7/18/2013	WW

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13077462	TRENTO ET AL.
	Examiner	**Art Unit**
	WALTER WEBB	1612

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	09/28/2012	11/20/2012	07/18/2013						
1	1	÷	✓	=						
2	2	÷	✓	=						
3	3	÷	✓	=						
4	4	÷	O	=						
5	5	÷	O	=						
6	6	÷	O	=						
7	7	÷	O	=						
8	8	÷	O	=						
9	9	÷	O	=						
	10	÷	O	-						
10	11	÷	O	=						
11	12	÷	O	=						
12	13	÷	O	=						
13	14	÷	O	=						
14	15	÷	O	=						
	16	÷	✓	-						
	17	÷	✓	-						
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19	27	÷	✓	=						
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	32	÷	O	-						
	33	÷	O	-						
	34	÷	N	-						
	35	÷	N	-						
	36	÷	N	-						

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13077462	TRENTO ET AL.
	Examiner	**Art Unit**
	WALTER WEBB	1612

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=	Allowed	÷	Restricted	I	Interference	O	Objected

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	09/28/2012	11/20/2012	07/18/2013						
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	38	÷	N	-						
	39	÷	N	-						
	40	÷	N	-						
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	49	÷	N	-						
	50	÷	O	-						
	51	÷	O	-						
24	52			=						
25	53			=						

PTO/SB/122 (11-08)
Approved for use through 11/30/2011. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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CHANGE OF CORRESPONDENCE ADDRESS
Application

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

Application Number	13/077,462
Filing Date	03/31/2011
First Named Inventor	Fabio Trento, Pare (Como), (IT)
Art Unit	1612
Examiner Name	Webb, Walter E.
Attorney Docket Number	23278.20 (US2) / 5608

Please change the Correspondence Address for the above-identified patent application to:

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This form cannot be used to change the data associated with a Customer Number. To change the data associated with an existing Customer Number use "Request for Customer Number Data Change" (PTO/SB/124).

I am the:

☐ Applicant/Inventor

☐ Assignee of record of the entire interest.
Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96).

☑ Attorney or agent of record. Registration Number 36,942.

☐ Registered practitioner named in the application transmittal letter in an application without an executed oath or declaration. See 37 CFR 1.33(a)(1). Registration Number_____.

Signature	\Clark G. Sullivan\
Typed or Printed Name	Clark G. Sullivan
Date 09/23/2013	Telephone (212) 704-6105

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☐ *Total of _____forms are submitted.

This collection of information is required by 37 CFR 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.

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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.

1612

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

EFS ID:	16949053
Application Number:	13077462
International Application Number:	
Confirmation Number:	5608
Title of Invention:	Compositions and Methods for Treating Centrally Mediated Nausea and Vomiting
First Named Inventor/Applicant Name:	Fabio Trento
Customer Number:	53449
Filer:	Clark G. Sullivan/Angelina Stantini
Filer Authorized By:	Clark G. Sullivan
Attorney Docket Number:	23278.20 (US2)
Receipt Date:	25-SEP-2013
Filing Date:	31-MAR-2011
Time Stamp:	11:51:40
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	Change of Address	13077462COCA.pdf	249149 92b11a5bbe32e3685cdd29970a7686962b3598d5	no	2

Warnings:	
Information:	

Total Files Size (in bytes):	249149

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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.: 244168.000015US2
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Fabio Trento et al.	Customer No.: 06980
Application No.: 13/077,462	Confirmation No.: 5608
Filing Date: March 31, 2011	Art Unit: 1612
For: Compositions and Methods for Treating Centrally Mediated Nausea and Vomiting	Examiner: WEBB, WALTER E

AMENDMENT AFTER ALLOWANCE UNDER 37 C.F.R. 1.312

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

Dear Sir:

INTRODUCTORY COMMENTS

Applicants thank the Examiner for the Notice of Allowance dated August 1, 2013. Prior to issuance of the patent, Applicants respectfully request entry of this amendment under 37 C.F.R. 1.312 for the above-identified application.

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

Remarks begin on page 6 of this paper.

AMENDMENTS TO THE CLAIMS

Please replace all prior listings of claims with the following listing:

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

a) administering to said patient on day one netupitant or a pharmaceutically acceptable salt thereof, in a therapeutically effective amount which enters the systemic circulation, crosses the blood brain barrier and occupies at least 70% of neurokinin-1 (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 palonosetron or a pharmaceutically acceptable salt thereof; and

c) administering to said patient on day one a first dose of dexamethasone which is ineffective against chemotherapy induced nausea and vomiting (CINV) when administered alone, but effective against CINV when administered in combination with said netupitant,

wherein said first dose of dexamethasone comprises from 50 to 70% of a minimum effective dose when administered alone against CINV;

steps (a), (b) and (c) are effective to treat both nausea and vomiting during the period defined by days one through five; and

steps (a), (b) and (c) are effective to treat both nausea and vomiting to a greater extent during the period defined by days one through five than steps (b) and (c) alone.

2) (Previously presented) 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 vomiting when administered alone against vomiting, but effective against vomiting when administered in combination with steps (a) and (b), wherein said second dose comprises from 40 to 60% of a minimum effective dose when administered alone against vomiting.

3) (Original) 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) (Previously presented) The method of claim 1, wherein only one dose of netupitant or a pharmaceutically acceptable salt thereof is administered during said five days.

5) (Previously presented) The method of claim 1, 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) (Previously presented) The method of claim 1, wherein said therapeutically effective amount of netupitant comprises from about 200 to about 400 mg of netupitant or a pharmaceutically acceptable salt thereof.

7) (Previously presented) The method of claim 1, wherein said therapeutically effective amount of netupitant comprises about 300mg of netupitant as a free base.

8) (Previously presented) The method of claim 1, wherein said therapeutically minimum effective dose of dexamethasone when administered alone comprises from about 16 mg to about 20 mg of dexamethasone.

9) (Previously presented) The method of claim 1, wherein only one dose of said palonosetron or a pharmaceutically acceptable salt thereof is administered during said five days.

10) (Canceled)

11) (Previously presented) The method claim 1, wherein said therapeutically effective amount of palonosetron or pharmaceutically acceptable salt thereof is from about 0.25 to about 0.75 mg based on the weight of the free base.

12) (Previously presented) The method of claim 1, wherein said palonosetron is administered as palonosetron hydrochloride, and said therapeutically effective amount of said palonosetron hydrochloride is about 0.56 mg of palonosetron hydrochloride, corresponding to about 0.5 mg of palonosetron as a free base.

13) (Previously presented) The method of claim 1, wherein said palonosetron is administered orally.

14) (Previously presented) The method of claim 1, 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) (Previously presented) The method of claim 1, 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)–22) (Canceled)

23) (Previously presented) The method of claim 1, 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 1, wherein said nausea and vomiting is induced by moderately or highly emetogenic chemotherapy.

25) (Previously presented) The method of claim 1, 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 1, 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) (Previously presented) A method of treating both nausea and vomiting in a human subject in need thereof during the acute or delayed phases of chemotherapy induced nausea and vomiting (CINV) in response to moderately or highly emetogenic chemotherapy, comprising administering to said subject before said chemotherapy 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.

28) (Previously presented) 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) (Currently Amended) The method of claim 27, comprising orally administering about 300 ~~mg.~~ mg of netupitant as the free base and about 0.56 mg of palonosetron hydrochloride.

30) (Currently Amended) The method of claim 27, further comprising, if said patient is undergoing highly emetogenic chemotherapy, administering a sub-therapeutic dose of dexamethasone on days one, two, three and four, wherein day one is the day on which netupitant and palonosetron, or pharmaceutically acceptable salts thereof, are administered.

31) (Currently Amended) The method of claim 27, 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, wherein day one is the day on which netupitant and palonosetron, or pharmaceutically acceptable salts thereof, are administered.

32)–51) (Canceled)

52) (Previously presented) The method of claim 1, wherein said netupitant or pharmaceutically acceptable salt thereof and said palonosetron or pharmaceutically acceptable salt thereof are synergistically effective to antagonize NK1 activity.

53) (Previously presented) The method of claim 27, wherein said netupitant or pharmaceutically acceptable salt thereof and said palonosetron or pharmaceutically acceptable salt thereof are synergistically effective to antagonize NK1 activity.

REMARKS

Applicants respectfully request entry of the amendments to Claims 29-31. The claims have been amended to correct formal matters in the claims without changing the scope thereof. Specifically, Claim 29 is amended to correct the obvious typographical error "mg." to "mg". Claims 30 and 31 are amended to add antecedent basis for the phrase "days one, two, three, and four" by adding the phrase "wherein day one is the day on which netupitant and palonosetron, or pharmaceutically acceptable salts thereof, are administered." Support for these amendments can be found in the claim from which they depend, claim 27, as well as the claims as originally filed and the specification.

It is believed that these amendments merely correct informalities and will not require a new search. No new matter has been added by way of these claim amendments. Applicants respectfully request that the amendments be entered.

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: October 29, 2013

Respectfully submitted,

/Heather Morehouse Ettinger/

Heather Morehouse Ettinger
Registration No.: 51658
Troutman Sanders LLP
The Chrysler Building
405 Lexington Avenue
New York, New York 10174
Direct Tel: (212) 704-6136
Fax: (212) 704-6288
Direct E-mail:
heather.ettinger@troutmansanders.com
Attorneys/Agents for Applicant

Electronic Acknowledgement Receipt

EFS ID:	17257363
Application Number:	13077462
International Application Number:	
Confirmation Number:	5608
Title of Invention:	Compositions and Methods for Treating Centrally Mediated Nausea and Vomiting
First Named Inventor/Applicant Name:	Fabio Trento
Customer Number:	6980
Filer:	Katherine Harihar/Angelina Stantini
Filer Authorized By:	Katherine Harihar
Attorney Docket Number:	23278.20 (US2) 5608
Receipt Date:	29-OCT-2013
Filing Date:	31-MAR-2011
Time Stamp:	16:02:20
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		US2-PTO-312AMENDMENT.pdf	85237 a102d1dd211670942af97cece429b339ca8ab343	yes	6

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment after Notice of Allowance (Rule 312)	1	1
	Claims	2	5
	Applicant Arguments/Remarks Made in an Amendment	6	6
Warnings:			
Information:			
	Total Files Size (in bytes):	85237	

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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.: 244168.000015US2
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Fabio Trento et al.	Customer No.: 06980
Application No.: 13/077,462	Confirmation No.: 5608
Filing Date: March 31, 2011	Art Unit: 1612
For: Compositions and Methods for Treating Centrally Mediated Nausea and Vomiting	Examiner: WEBB, WALTER E

PETITION FOR UNINTENTIONALLY DELAYED DOMESTIC BENEFIT CLAIM UNDER 37 C.F.R. § 1.78(a)(3)

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

Dear Sir:

Applicants respectfully submit this Petition under 37 C.F.R. § 1.78(a)(3) for acceptance of an unintentionally delayed claim under 35 U.S.C. § 120 for the benefit of a prior-filed co-pending international application.

Applicants respectfully request that the chain of priority in the present application is corrected to indicate that the present application is a continuation of International Application No. PCT/IB10/03106 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.

In accordance with 37 C.F.R. § 1.78(a)(3):

(i) The reference required by 35 U.S.C. § 120 and 37 C.F.R. § 1.78(a)(2) to prior-filed International Application No. PCT/IB10/03106 was previously submitted on August 18, 2011. Out of an abundance of caution, it is submitted again with this Petition in the form of an amended Application Data Sheet and an Amendment After Allowance under 37 C.F.R. 1.312.

(ii) The surcharge set forth in § 1.17(t) is being paid herewith.

(iii) Applicants hereby state that the entire delay between the date the claim was due under 37 C.F.R. § 1.78(a)(2)(ii) and the date this claim is filed was unintentional.

Applicants submit concurrently an amendment to the specification to provide an appropriate incorporation by reference. Applicants also submit a Supplemental Application Data Sheet indicating the correct priority information.

Applicants respectfully request to amend the chain of priority in the present application to read as recited in the amendment and the Supplemental Application Data Sheet submitted herewith. Should the Examiner have any questions, the Examiner is invited to call the undersigned.

Applicants reserve their right to question the propriety of the Office's refusal to acknowledge their priority claim based on their diligent efforts to satisfy the Office's requirements, and their position that PCT/IB10/03106 and PCT/US10/57192 are one and the same application, differing only by the number assigned to them by the United States Patent Office and World International Property Organization.

Early and favorable consideration of this petition is earnestly solicited.

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: November 1, 2013

Respectfully submitted,

/Clark G. Sullivan/

Clark G. Sullivan
Registration No.: 36942
Troutman Sanders LLP
The Chrysler Building
405 Lexington Avenue
New York, New York 10174
Direct Tel: (212) 704-6105
Fax: (212) 704-6288
Direct E-mail:
clark.sullivan@troutmansanders.com
Attorneys/Agents for Applicant

Docket No.: 244168.000015US2
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Fabio Trento et al.	Customer No.: 06980
Application No.: 13/077,462	Confirmation No.: 5608
Filing Date: March 31, 2011	Art Unit: 1612
For: Compositions and Methods for Treating Centrally Mediated Nausea and Vomiting	Examiner: WEBB, WALTER E

AMENDMENT AFTER ALLOWANCE UNDER 37 C.F.R. 1.312

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

Dear Sir:

INTRODUCTORY COMMENTS

Applicants thank the Examiner for the Notice of Allowance dated August 1, 2013. Prior to issuance of the patent, Applicants respectfully request entry of this amendment under 37 C.F.R. 1.312 for the above-identified application.

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

Remarks begin on page 3 of this paper.

AMENDMENTS TO THE SPECIFICATION

On Page 1 of the Specification, please replace the paragraph after the heading "CROSS-REFERENCE TO RELATED APPLICATIONS", as amended on August 18, 2011, with the following paragraph:

This application is a continuation of International Patent Application No. PCT/IB10/03106, 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. Application Nos. 61/262,470 and 61/382,709 ~~and PCT Application No. PCT/IB10/03106~~ are hereby incorporated herein by reference in their entirety.

REMARKS

Applicants respectfully request entry of the amendment to the specification. It is believed that this amendment merely corrects informalities and will not require a new search. No new matter has been added by way of these claim amendments. Applicants respectfully request that the amendment be entered.

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: November 1, 2013

Respectfully submitted,

/Clark G. Sullivan/

Clark G. Sullivan
Registration No.: 36942
Troutman Sanders LLP
The Chrysler Building
405 Lexington Avenue
New York, New York 10174
Direct Tel: (212) 704-6105
Fax: (212) 704-6288
Direct E-mail:
clark.sullivan@troutmansanders.com
Attorneys/Agents for Applicant

PTO/SB/14 (11-08)
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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	23278.20
	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.)

Applicant Information:

Applicant 1

Applicant Authority	◉ Inventor	○ Legal Representative under 35 U.S.C. 117	○ Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
	Fabio		Trento	

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

City	Como	Country Of Residence	IT
Citizenship under 37 CFR 1.41(b)	IT		

Mailing Address of Applicant:

Address 1	Via Alla Valle 20B		
Address 2	Paré		
City	Como	State/Province	
Postal Code	I-22020	Country	IT

Applicant 2

Applicant Authority	◉ Inventor	○ Legal Representative under 35 U.S.C. 117	○ Party of Interest under 35 U.S.C. 118

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	CH
Citizenship under 37 CFR 1.41(b)	CH		

Mailing Address of Applicant:

Address 1	Via Sarone 21A		
Address 2			
City	Cagiallo	State/Province	
Postal Code	CH6955	Country	CH

Applicant 3

Applicant Authority	◉ Inventor	○ Legal Representative under 35 U.S.C. 117	○ Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
	Giorgia		Rossi	

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

City	Como	Country Of Residence	IT

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	23278.20
	Application Number	
Title of Invention	Compositions and Methods for Treating Centrally Mediated Nausea and Vomiting	

Citizenship under 37 CFR 1.41(b)	IT			
Mailing Address of Applicant:				
Address 1	Via della Libertá, 1A			
Address 2	Cernobbio			
City	Como	**State/Province**		
Postal Code	I-22012	**Country**	IT	

Applicant 4

Applicant Authority	(•) Inventor	( ) Legal Representative under 35 U.S.C. 117	( ) Party of Interest under 35 U.S.C. 118	
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**	IT
Citizenship under 37 CFR 1.41(b)	IT		

Mailing Address of Applicant:

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

Applicant 5

Applicant Authority	(•) Inventor	( ) Legal Representative under 35 U.S.C. 117	( ) Party of Interest under 35 U.S.C. 118	
Prefix	**Given Name**	**Middle Name**	**Family Name**	**Suffix**
	Daniele		Bonadeo	

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

City	Varese	**Country Of Residence**	IT
Citizenship under 37 CFR 1.41(b)	IT		

Mailing Address of Applicant:

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

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	53449

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	23278.20
	Application Number	
Title of Invention	Compositions and Methods for Treating Centrally Mediated Nausea and Vomiting	

Email Address	patents@agg.com	Add Email	Remove Email

Application Information:

Title of the Invention	Compositions and Methods for Treating Centrally Mediated Nausea and Vomiting		
Attorney Docket Number	23278.20	**Small Entity Status Claimed**	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Suggested Class (if any)		**Sub Class (if any)**	
Suggested Technology Center (if any)			
Total Number of Drawing Sheets (if any)		**Suggested Figure for Publication (if any)**	

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). Enter either Customer Number or complete the Representative Name section below. If both sections are completed the Customer Number will be used for the Representative Information during processing.

Please Select One:	◉ Customer Number	○ US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	53449		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, or 365(c) or indicate National Stage entry from a PCT application. Providing this 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(a)(2) or CFR 1.78(a)(4), and need not otherwise be made part of the specification.

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	Continuation of	~~PCT/US10/57192~~ PCT/IB10/03106	~~2010-11-19~~ 2010-11-18
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
~~PCT/US10/57192~~ PCT/IB10/03106	non provisional of	61382709	2010-09-14
Prior Application Status	Expired		Remove

PTO/SB/14 (11-08)
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	23278.20
	Application Number	
Title of Invention	Compositions and Methods for Treating Centrally Mediated Nausea and Vomiting	

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
~~PCT/US10/57192~~ PCT/IB10/03106	non provisional of	61262470	2009-11-18

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

Foreign Priority Information:

This section allows for the applicant to claim benefit of foreign priority and to identify any prior foreign application for which priority is not claimed. 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(a).

Remove

Application Number	Country	Parent Filing Date (YYYY-MM-DD)	Priority Claimed
			◉ Yes ○ No

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

Assignee Information:

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

Assignee 1

If the Assignee is an Organization check here. ☒

Organization Name	Helsinn Healthcare S.A.		
Mailing Address Information:			
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 Assignee Data may be generated within this form by selecting the **Add** button.

Signature:

A signature of the applicant or representative is required in accordance with 37 CFR 1.33 and 10.18. Please see 37 CFR 1.4(d) for the form of the signature.

Signature	/Clark G. Sullivan/			Date (YYYY-MM-DD)	2013-11-01
First Name	Clark G.	Last Name	Sullivan	Registration Number	36942

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	23278.20
	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 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:	13077462
Filing Date:	31-Mar-2011
Title of Invention:	Compositions and Methods for Treating Centrally Mediated Nausea and Vomiting
First Named Inventor/Applicant Name:	Fabio Trento
Filer:	Clark G. Sullivan/Angelina Stantini
Attorney Docket Number:	23278.20 (US2) 5608

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Priority Accept. Unintent. Delayed Claim	1454	1	1420	1420
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**1420**

Electronic Acknowledgement Receipt

EFS ID:	17290881
Application Number:	13077462
International Application Number:	
Confirmation Number:	5608
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/Angelina Stantini
Filer Authorized By:	Clark G. Sullivan
Attorney Docket Number:	23278.20 (US2) 5608
Receipt Date:	01-NOV-2013
Filing Date:	31-MAR-2011
Time Stamp:	13:22:03
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$1420
RAM confirmation Number	11200
Deposit Account	201507
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Petition for review by the Office of Petitions.	US2-PTO-PETITION.PDF	682008 99999bad80a1c8fe506d3c3efe58df1f9e5bd81b	no	11
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30321 26e744a3f626b43c9dbbec59b332b34ba7cfeb26	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	712329		

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.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

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

53449 7590 08/01/2013
PATENT CORRESPONDENCE
ARNALL GOLDEN GREGORY LLP
171 17TH STREET NW
SUITE 2100
ATLANTA, GA 30363

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

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

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/077,462	03/31/2011	Fabio Trento	23278.20 (US2)	5608

TITLE OF INVENTION: Compositions and Methods for Treating Centrally Mediated Nausea and Vomiting

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$890	$300	$0	$1190	11/01/2013

EXAMINER	ART UNIT	CLASS-SUBCLASS
WEBB, WALTER E	1612	514-017700

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

☒ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,

(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 Clark G. Sullivan
2 Heather M. Ettinger
3 Troutman Sanders LLP

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: Helsinn Healthcare S.A.

(B) RESIDENCE: (CITY and STATE OR COUNTRY): Lugano/Pazzallo, Switzerland

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:

☒ Issue Fee

☒ Publication Fee (No small entity discount permitted)

☐ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**

☐ A check is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☒ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number 201507 (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)

☐ Applicant certifying micro entity status. See 37 CFR 1.29	NOTE: Absent a valid certification of Micro Entity Status (see form PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
☐ Applicant asserting small entity status. See 37 CFR 1.27	NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
☒ Applicant changing to regular undiscounted fee status.	NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature /Clark G. Sullivan/ Date November 1, 2013

Typed or printed name Clark G. Sullivan Registration No. 36942

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 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, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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CHANGE OF CORRESPONDENCE ADDRESS
Application

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

Application Number	13/077,462
Filing Date	03-31-2011
First Named Inventor	Fabio Trento
Art Unit	1612
Examiner Name	WEBB, WALTER E
Attorney Docket Number	23278.20 (US2) 5608

Please change the Correspondence Address for the above-identified patent application to:

☑ The address associated with Customer Number: 06980

OR

☐ Firm or Individual Name

Address

City	State	Zip

Country

Telephone	Email

This form cannot be used to change the data associated with a Customer Number. To change the data associated with an existing Customer Number use "Request for Customer Number Data Change" (PTO/SB/124).

I am the:

☐ Applicant/Inventor

☐ Assignee of record of the entire interest.
Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96).

☑ Attorney or agent of record. Registration Number 36942.

☐ Registered practitioner named in the application transmittal letter in an application without an executed oath or declaration. See 37 CFR 1.33(a)(1). Registration Number_____.

Signature	/Clark G. Sullivan/
Typed or Printed Name	Clark G. Sullvan, Reg. No. 36942
Date November 1, 2013	Telephone 212-704-6105

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☐ *Total of _____forms are submitted.

This collection of information is required by 37 CFR 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 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.

Electronic Patent Application Fee Transmittal

Application Number:	13077462
Filing Date:	31-Mar-2011
Title of Invention:	Compositions and Methods for Treating Centrally Mediated Nausea and Vomiting
First Named Inventor/Applicant Name:	Fabio Trento
Filer:	Clark G. Sullivan/Angelina Stantini
Attorney Docket Number:	23278.20 (US2) 5608

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

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:				
Utility Appl Issue Fee	1501	1	1780	1780
Publ. Fee- Early, Voluntary, or Normal	1504	1	300	300

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**2080**

Electronic Acknowledgement Receipt

EFS ID:	17292317
Application Number:	13077462
International Application Number:	
Confirmation Number:	5608
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/Angelina Stantini
Filer Authorized By:	Clark G. Sullivan
Attorney Docket Number:	23278.20 (US2) 5608
Receipt Date:	01-NOV-2013
Filing Date:	31-MAR-2011
Time Stamp:	14:38:08
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$2080
RAM confirmation Number	885
Deposit Account	201507
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Issue Fee Payment (PTO-85B)	US2-PTO-ISSUEFEE.PDF	141958 86368b45926568776ba18fda8b1390ff61accaa5	no	2
Warnings:					
Information:					
2	Change of Address	US2-PTO-CHANGE.PDF	159690 cf4f44145eed9cd29c564564a4002671d83272e3	no	2
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	31757 bb8c75cf4a268054f6ec5c5178c7c882beebd259	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	333405		

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.: 244168.000015US2
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Fabio Trento et al.	Customer No.: 06980
Application No.: 13/077,462	Confirmation No.: 5608
Filing Date: March 31, 2011	Art Unit: 1612
For: Compositions and Methods for Treating Centrally Mediated Nausea and Vomiting	Examiner: WEBB, WALTER E

AMENDMENT AFTER ALLOWANCE UNDER 37 C.F.R. 1.312

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

OK TO ENTER: /W.W./

Dear Sir:

INTRODUCTORY COMMENTS

Applicants thank the Examiner for the Notice of Allowance dated August 1, 2013. Prior to issuance of the patent, Applicants respectfully request entry of this amendment under 37 C.F.R. 1.312 for the above-identified application.

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

Remarks begin on page 6 of this paper.

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/077,462	01/07/2014	8623826	23278.20 (US2) 5608	5608

6980 7590 12/18/2013

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

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

Fabio Trento, Pare (Como), ITALY;
Sergio Cantoreggi, Cagiallo, SWITZERLAND;
Giorgia Rossi, Cernobbio (Como), ITALY;
Roberta Cannella, Varese, ITALY;
Daniele Bonadeo, Casalzuigno, ITALY;

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