

REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL **(Submitted Only via EFS-Web)**

Application Number	15003327	Filing Date	2016-01-21	Docket Number (if applicable)	HHC002US6/CO001	Art Unit	1612
First Named Inventor	Fabio TRENTO			Examiner Name	WEBB, WALTER E		

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.

Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. The Instruction Sheet for this form is located at WWW.USPTO.GOV

SUBMISSION REQUIRED UNDER 37 CFR 1.114

Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____

☐ Other _____

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☒ Amendment/Reply

☐ Information Disclosure Statement (IDS)

☐ Affidavit(s)/ Declaration(s)

☐ Other _____

MISCELLANEOUS

☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of months _____
 (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

☐ Other _____

FEES

☒ The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.
 The Director is hereby authorized to charge any underpayment of fees, or credit any overpayments, to
 Deposit Account No 600254

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

☒ Patent Practitioner Signature

Applicant Signature

Signature of Registered U.S. Patent Practitioner			
Signature	Clark G. Sullivan/	Date (YYYY-MM-DD)	2017-01-02
Name	Clark G. Sullivan	Registration Number	36942

This collection of information is required by 37 CFR 1.114. 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.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:	)	
Trento et al.	)	Customer No.: 140619
	)	
Application No.: 15/003,327	)	Confirmation No.: 1097
	)	
Filing Date: 01-21-2016	)	Art Unit: 1612
	)	
For: COMPOSITIONS AND METHODS FOR	)	Examiner: WEBB, WALTER E.
TREATING CENTRALLY MEDIATED	)	
NAUSEA AND VOMITING	)	

AMENDMENT TO ACCOMPANY REQUEST FOR CONTINUING EXAMINATION

Commissioner for Patents
Alexandria, VA 22313-1450

Dear Sir:

In response to the Final Rejection notified in the above-referenced application on September 1, 2016, and further to the Advisory Action mailed on December 21, 2016, please enter the following amendments and consider the following remarks.

A REPLACEMENT CLAIM SET begins on page 2.

REMARKS begin on page 6.

REPLACEMENT CLAIM SET

1)-15) (CANCELED)

- 16) (CURRENTLY AMENDED) A method of treating nausea and vomiting from an emesis-inducing event for a period of five consecutive days in a patient in need thereof, comprising administering to said patient netupitant or a pharmaceutically acceptable salt thereof, in a therapeutically effective amount which is effective to treat nausea and vomiting during the acute and delayed phases of emesis, and which enters the systemic circulation, crosses the blood brain barrier and occupies 70% or more of NK₁ receptors in the striatum seventy-two hours after said administration, wherein ~~said therapeutically effective dose comprises~~ a single dose of netupitant or pharmaceutically acceptable salt thereof is administered on day one of said five consecutive days, no further netupitant or pharmaceutically acceptable salt thereof is administered during said five consecutive days, and said single dose of netupitant or pharmaceutically acceptable salt thereof is effective to treat said nausea and vomiting for said five consecutive days.
- 17) (PREVIOUSLY PRESENTED) The method of claim 16, wherein said netupitant occupies 80% or more of NK₁ receptors in the striatum seventy-two hours after said administration.
- 18) (PREVIOUSLY PRESENTED) The method of claim 16, further comprising: a) administering to said patient on day one a first dose of dexamethasone which is ineffective against nausea and vomiting when administered alone, but effective against nausea and vomiting when administered in combination with said netupitant, wherein said first dose comprises from 50 to 70% of a minimum effective dose when administered alone; and b) if said patient is subject to highly emetogenic chemotherapy, administering to said patient, on days two, three and four, a second dose of dexamethasone which is ineffective against nausea and vomiting when administered alone, but effective against nausea and vomiting when administered in combination with said netupitant, wherein said second dose comprises from 40 to 60% of a minimum effective dose when administered alone.
- 19) (CANCELED)
- 20) (CANCELED)

- 21) (PREVIOUSLY PRESENTED) The method of claim 16 wherein: a) only one dose of netupitant is administered during said five days on day one, comprising about 300 mg. of netupitant as the free base; and b) administering about 12 mg. of dexamethasone on day one; and c) if said patient is undergoing highly emetogenic chemotherapy, administering about 8 mg. of dexamethasone on days two, three and four.
- 22) (CANCELED)
- 23) (PREVIOUSLY PRESENTED) The method of claim 16 wherein said nausea and vomiting is chemotherapy induced nausea and vomiting ("CINV"), radiation therapy induced nausea and vomiting ("RINV"), or post-operative nausea and vomiting ("PONV").
- 24) (PREVIOUSLY PRESENTED) The method of claim 16 wherein said nausea and vomiting is induced by moderately or highly emetogenic chemotherapy.
- 25) (PREVIOUSLY PRESENTED) The method of claim 16 comprising administering moderately or highly emetogenic chemotherapy within from about one hour to about two hours of said administration of said netupitant or pharmaceutically acceptable salt thereof.
- 26) (PREVIOUSLY PRESENTED) The method of claim 16 comprising treating nausea and vomiting in response to highly emetogenic chemotherapy during the acute phase, or in response to highly emetogenic chemotherapy during the delayed phase, or in response to moderately emetogenic chemotherapy during the acute phase, or in response to moderately emetogenic chemotherapy during the delayed phase.
- 27) -51) (CANCELED)
- 52) (PREVIOUSLY PRESENTED) The method of claim 16, comprising orally administering from about 200 to about 400 mg of netupitant as the free base.
- 53) (PREVIOUSLY PRESENTED) The method of claim 16, comprising orally administering about 300 mg of netupitant as the free base.
- 54) (CURRENTLY AMENDED) A method of treating nausea and vomiting in response to an emesis-inducing event for a period of five consecutive days in a patient in need thereof, comprising administering to said patient netupitant or a pharmaceutically acceptable salt thereof, in a therapeutically effective amount which is effective to treat nausea and vomiting during the acute and delayed phases of emesis, wherein said therapeutically

effective amount of netupitant or pharmaceutically acceptable salt thereof is administered on day one of said five consecutive days, no further netupitant or pharmaceutically acceptable salt thereof is administered during said five consecutive days, and said single dose of netupitant or pharmaceutically acceptable salt thereof is effective to treat said nausea and vomiting for said five consecutive days.

- 55) (PREVIOUSLY PRESENTED) The method of claim 54, comprising orally administering from about 200 to about 400 mg of netupitant as the free base.
- 56) (PREVIOUSLY PRESENTED) The method of claim 54, comprising orally administering about 300 mg of netupitant as the free base.
- 57) (NEW) A method of treating chemotherapy induced nausea and vomiting (CINV) for five consecutive days comprising a single instance of inducing in a subject receiving chemotherapy blood levels of netupitant effective to treat said CINV prior to administration of chemotherapy to said subject, wherein said inducing event is effective to treat said nausea and vomiting for said five consecutive days.
- 58) (NEW) The method of claim 57, wherein when said chemotherapy is highly emetic chemotherapy, the chemotherapy is selected from the group consisting of carmustine, cisplatin, cyclophosphamide $\geq 1500 \text{ mg/m}^2$, dacarbazine, dactinomycin, mechlorethamine, streptozotocin and combinations thereof.
- 59) (NEW) The method of claim 57, wherein when said chemotherapy is moderately emetic chemotherapy, the chemotherapy is selected from the group consisting of carboplatin, cyclophosphamide $< 1500 \text{ mg/m}^2$, cytarabine $> 1 \text{ mg/m}^2$, daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, oxaliplatin and combinations thereof.
- 60) (NEW) The method of claim 57, wherein said chemotherapy is selected from the group consisting of carboplatin, cyclophosphamide, cytarabine $> 1 \text{ mg/m}^2$, daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, carmustine, cisplatin, dacarbazine, dactinomycin, mechlorethamine, streptozotocin, oxaliplatin and combinations thereof.
- 61) (NEW) The method of claim 57, wherein said treatment of CINV is defined as no emetic episodes and no use of rescue medication following said chemotherapy.

- 62) (NEW) The method of claim 57, wherein: a) said blood levels are induced by an intravenous anti-emetic regimen administered prior to said chemotherapy; and b) said regimen is effective to treat said CINV for a five-day period after said chemotherapy.
- 63) (NEW) The method of claim 57, wherein: a) said treatment of CINV is defined as no emetic episodes and no use of rescue medication following said chemotherapy b) said blood levels are induced by an intravenous anti-emetic regimen administered prior to said chemotherapy; and c) said regimen is effective to treat said CINV for a five-day period after said chemotherapy.
- 64) (NEW) The method of claim 63, wherein said netupitant occupies at least 70% of said patient's striatum NK1 receptors ninety-six hours after said administration.
- 65) (NEW) The method of claim 63, wherein said chemotherapy is highly emetogenic chemotherapy, said netupitant blood levels are effective to treat said CINV during the acute and delayed phases of said CINV, and said palonosetron blood levels are effective to treat said CINV during the acute phase of said CINV.
- 66) (NEW) The method of claim 63, wherein said chemotherapy is moderately emetogenic chemotherapy, said netupitant blood levels are effective to treat said CINV during the acute and delayed phases of said CINV, and said palonosetron blood levels are effective to treat said CINV during the acute phase of said CINV.
- 67) (NEW) The method of claim 63, wherein said chemotherapy is highly emetogenic chemotherapy, and said regimen is effective to prevent or reduce the severity of nausea during the acute and delayed phases.
- 68) (NEW) The method of claim 63, wherein said chemotherapy is moderately emetogenic chemotherapy, and said regimen is effective to prevent or reduce the severity of nausea during the acute and delayed phases.
- 69) (NEW) The method of claim 63, wherein said chemotherapy comprises cisplatin.
- 70) (NEW) The method of claim 63, wherein said chemotherapy comprises carboplatin, cisplatin, oxaliplatin, or doxorubicin.
- 71) (NEW) The method of claim 63, wherein said chemotherapy comprises cyclophosphamide.

REMARKS

Status of Claims

After the amendment, claims 16-18, 21, 23-26, and 52-71 are pending. Claims 16 and 54 are amended to further clarify that only one dose of netupitant is administered during the five-day period of acute and delayed emesis, and that this single dose is effecting throughout the five day time period. Claims 57-71 are added based generally on claims 4 *et seq.* from U.S. Patent No. 9,186,357, but omitting the requirement for palonosetron administration. No new matter is added by the amendment.

Response to Advisory Action

In the Advisory Action, the Examiner objected to the newly added language “wherein said therapeutically effective dose consists of a single dose of netupitant.” According to the Examiner, the netupitant must also be administered with other excipients. While Applicant disagrees with the Examiner’s interpretation of the claim, it has amended the claims to rule out this interpretation entirely, and to focus on the fact that one single dose of netupitant is administered over a five-day period of time, and the single dose is effective to prevent nausea and vomiting during the entire five-day period.

The Examiner also states that the claim raises potential enablement and written description issues. Applicant is not entirely clear what the Examiner is alluding to, but notes that the 5-day effectiveness is clearly described in the specification and proven in the examples. See Summary of Invention (“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”); Table 5 (reporting that the addition of 300 mg of netupitant to a single dose of palonosetron improves the patient’s response to chemotherapy during the acute (0-24 hours) and delayed phases (24-120 hours)).

In the Advisory Action, the Examiner also maintained that the amendment failed to place the application in a condition for allowance. Applicant’s position is that it is unexpected that a single dose of netupitant would be effective against nausea and vomiting during the acute and

delayed phases of emesis. In support of this position, Applicant cited the FDA-approved prescribing information for Emend[®], which discloses Emend[®] dosing on days 1, 2 and 3.

In response, the Examiner argues that

“The treatment of acute and delayed phases appears to be a property of administering the NK1. The claims states that treatment on day one but that does not necessarily exclude treatment on any other day of the five days. Again, because the prior art teaches treating 1-5 days, administration on day one would have been obvious.”

The Examiner takes the position that the claims do not exclude the potential for treatment on other days, but they plainly do. The claims affirmatively state that only one dose of netupitant is administered during the five-day period. The Examiner might be suggesting that other drugs can be administered during the five-day period, but that argument misses the point. Table 5 in the specification shows that a single 300 mg dose of netupitant independently provides protection against nausea and vomiting for five consecutive days, regardless of whether other drugs are administered. This ability to treat nausea and vomiting for 5 days from a single dose of netupitant, when the prior art teachings that other NK1 antagonists must be administered three times during the five-day period, is plainly unexpected, and proves that the claimed invention is non-obvious.

The Examiner also appears to make an inherency argument, but that argument also misses the point. To establish a prima facie case of obviousness, the Examiner bears the burden of proving that a worker of ordinary skill would have been motivated to administer netupitant only once, when the prior art taught that other NK1 antagonists must be administered 3 times. The claimed invention is not obvious because nothing in the prior art would have motivated a worker of ordinary skill in the art to administer netupitant only once during the five-day period. The invention only becomes obvious in hindsight, based on Applicant's teachings that a single dose of netupitant is effective during this entire five-day period.

CONCLUSION

Applicant respectfully submits that the application is in condition for allowance. If there is any fee due in connection with this filing, please charge the fee to Deposit Account No. 600254.

Respectfully submitted,

Sullivan IP Solutions, LLC
PO Box 2252
New York NY 10163
404.483.9360

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

Customer No. 140619

Electronic Patent Application Fee Transmittal				
Application Number:		15003327		
Filing Date:		21-Jan-2016		
Title of Invention:		COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING		
First Named Inventor/Applicant Name:		Fabio TRENTO		
Filer:		Clark G. Sullivan		
Attorney Docket Number:		HHC002US6/CO001		
Filed as Large Entity				
Filing Fees for Utility under 35 USC 111(a)				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Extension - 1 month with \$0 paid	1251	1	200	200
Miscellaneous:				
RCE- 1st Request	1801	1	1200	1200
Total in USD (\$)				1400

Electronic Acknowledgement Receipt

EFS ID:	27943880
Application Number:	15003327
International Application Number:	
Confirmation Number:	1097
Title of Invention:	COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING
First Named Inventor/Applicant Name:	Fabio TRENTO
Customer Number:	140619
Filer:	Clark G. Sullivan
Filer Authorized By:	
Attorney Docket Number:	HHC002US6/CO001
Receipt Date:	02-JAN-2017
Filing Date:	21-JAN-2016
Time Stamp:	17:33:43
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	\$ 1400
RAM confirmation Number	010317INTEFSW17343300
Deposit Account	
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Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Request for Continued Examination (RCE)	US6_RCE.pdf	697616	no	3
			7ea0e1357ac1be2d9349727e9f5b686291a cfc0b		
Warnings:					
Information:					
2		US6_1_2017_RCE_Amendment .pdf	101462	yes	8
			d57d3867b60acc1654a4dc61a703d33833b 74b17		
	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Amendment Submitted/Entered with Filing of CPA/RCE		1	1	
	Claims		2	5	
	Applicant Arguments/Remarks Made in an Amendment		6	8	
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	32527	no	2
			49b438d5c359a10709f120d5d5e8eb09e63 237f6		
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☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____

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☒ Enclosed

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☐ Information Disclosure Statement (IDS)

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SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

☒ Patent Practitioner Signature

Applicant Signature

Signature of Registered U.S. Patent Practitioner			
Signature	Clark G. Sullivan/	Date (YYYY-MM-DD)	2017-01-02
Name	Clark G. Sullivan	Registration Number	36942

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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.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 15/003,327	Filing Date 01/21/2016	☐ To be Mailed
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ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

(Column 1)

(Column 2)

FOR	NUMBER FILED	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

(Column 1)

(Column 2)

(Column 3)

AMENDMENT	01/02/2017	CLAIMS REMAINING AFTER AMENDMENT	MINUS	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)	ADDITIONAL FEE (\$)
	Total (37 CFR 1.16(i))	* 27	Minus	** 28	= 0	X \$80 =	0
	Independent (37 CFR 1.16(h))	* 3	Minus	*** 3	= 0	X \$420 =	0
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	0

(Column 1)

(Column 2)

(Column 3)

AMENDMENT	CLAIMS REMAINING AFTER AMENDMENT	MINUS	HIGHEST NUMBER PREVIOUSLY PAID FOR	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
CAROLYN THOMAS

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/003,327	01/21/2016	Fabio TRENTO	HHC002US6/CO001	1097
140619	7590	03/13/2017		
Sullivan IP Solutions, LLC PO Box 2252 New York, NY 10163			EXAMINER WEBB, WALTER E	
			ART UNIT	PAPER NUMBER
			1612	
			NOTIFICATION DATE	DELIVERY MODE
			03/13/2017	ELECTRONIC

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

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

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

clark@sullivanipsolutions.com
docketing@sullivanipsolutions.com

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

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

Period for Reply

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

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

Status

- 1) ☒ Responsive to communication(s) filed on 1/2/2017.
☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
- 4) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

- 5) ☒ Claim(s) 16-18,21,23-26 and 52-71 is/are pending in the application.
5a) Of the above claim(s) 57-71 is/are withdrawn from consideration.
- 6) ☐ Claim(s) _____ is/are allowed.
- 7) ☒ Claim(s) 16-18,21,23-26 and 52-56 is/are rejected.
- 8) ☐ Claim(s) _____ is/are objected to.
- 9) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

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

Application Papers

- 10) ☐ The specification is objected to by the Examiner.
- 11) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

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

Certified copies:

- a) ☐ All b) ☐ Some** c) ☐ None of the:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

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

Attachment(s)

- | | |
|---|---|
| 1) ☐ Notice of References Cited (PTO-892) | 3) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b)
Paper No(s)/Mail Date _____ | 4) ☐ Other: _____ |

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/2/2017 has been entered.

Applicants' arguments, filed 1/2/2017, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Election/Restrictions

Newly submitted claims 57-71 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: it is drawn to an "inducing event" for treating nausea and vomiting.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 57-71 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Nonstatutory Obvious-type Double Patenting

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

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

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

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

2) Claims 16-18, 21, 23-26, 52-56 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-62 of U.S. Patent No. 9,186,357. Although the claims at issue are not identical, they are not patentably distinct from each

Art Unit: 1612

other because the both claim a method of treating nausea and vomiting by administering netupitant.

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

Response to Arguments

No argument were made in regard to the ODP rejections.

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.

Art Unit: 1612

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

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

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

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

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

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

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REMARKS

Status of Claims

After the amendment, claims 16-18, 21, 23-26, 52-56, 58-61, 64, and 67-71 are pending. No new matter is added by the amendment.

Response to Office Action

In the Office Action, the Examiner objects to newly added claims 57-71 because they allegedly are inconsistent with the election Applicant made previously in response to a restriction requirement. Applicant has amended the claims so that claims 16 and 54 are the only two independent claims and trusts it has addressed the objection.

The Examiner also rejects the claims for obviousness type double patenting over US Patent Nos. 8,623,826, 9,186,357, and 9,271,975. In response, Applicant has filed a terminal disclaimer over these earlier patents and trusts it has overcome the rejection.

CONCLUSION

Applicant respectfully submits that the application is in condition for allowance. If there is any fee due in connection with this filing, please charge the fee to Deposit Account No. 600254.

Respectfully submitted,

Sullivan IP Solutions, LLC
PO Box 2252
New York NY 10163
404.483.9360

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

Customer No. 140619

Electronic Acknowledgement Receipt

EFS ID:	29474507
Application Number:	15003327
International Application Number:	
Confirmation Number:	1097
Title of Invention:	COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING
First Named Inventor/Applicant Name:	Fabio TRENTO
Customer Number:	140619
Filer:	Clark G. Sullivan
Filer Authorized By:	
Attorney Docket Number:	HHC002US6/CO001
Receipt Date:	13-JUN-2017
Filing Date:	21-JAN-2016
Time Stamp:	09:04:22
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no
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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		US6_6_2017_Amendment.pdf	84966	yes	6
			d7f972a470256424d440a4de7f557f5569c56558		

Multipart Description/PDF files in .zip description			
Document Description	Start	End	
Applicant Arguments/Remarks Made in an Amendment	1	1	
Claims	2	5	
Amendment/Req. Reconsideration-After Non-Final Reject	6	6	

Warnings:

Information:

Total Files Size (in bytes):	84966
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This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for 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 THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:	)	
Trento et al.	)	Customer No.: 140619
	)	
Application No.: 15/003,327	)	Confirmation No.: 1097
	)	
Filing Date: January 21, 2016	)	Art Unit: 1612
	)	
For: COMPOSITIONS AND METHODS FOR	)	Examiner: WEBB, WALTER E.
TREATING CENTRALLY MEDIATED	)	
NAUSEA AND VOMITING	)	

AMENDMENT AND RESPONSE TO OFFICE ACTION

Commissioner for Patents
Alexandria, VA 22313-1450

Dear Sir:

In response to the Office Action notified in the above-referenced application on March 13, 2017, please enter the following amendments and consider the following remarks.

A REPLACEMENT CLAIM SET begins on page 2.

REMARKS begin on page 6.

REPLACEMENT CLAIM SET

1)-15) (CANCELED)

- 16) (PREVIOUSLY PRESENTED) A method of treating nausea and vomiting from an emesis-inducing event for a period of five consecutive days in a patient in need thereof, comprising administering to said patient netupitant or a pharmaceutically acceptable salt thereof, in a therapeutically effective amount which is effective to treat nausea and vomiting during the acute and delayed phases of emesis, and which enters the systemic circulation, crosses the blood brain barrier and occupies 70% or more of NK₁ receptors in the striatum seventy-two hours after said administration, wherein a single dose of netupitant or pharmaceutically acceptable salt thereof is administered on day one of said five consecutive days, no further netupitant or pharmaceutically acceptable salt thereof is administered during said five consecutive days, and said single dose of netupitant or pharmaceutically acceptable salt thereof is effective to treat said nausea and vomiting for said five consecutive days.
- 17) (PREVIOUSLY PRESENTED) The method of claim 16, wherein said netupitant occupies 80% or more of NK₁ receptors in the striatum seventy-two hours after said administration.
- 18) (PREVIOUSLY PRESENTED) The method of claim 16, further comprising: a) administering to said patient on day one a first dose of dexamethasone which is ineffective against nausea and vomiting when administered alone, but effective against nausea and vomiting when administered in combination with said netupitant, wherein said first dose comprises from 50 to 70% of a minimum effective dose when administered alone; and b) if said patient is subject to highly emetogenic chemotherapy, administering to said patient, on days two, three and four, a second dose of dexamethasone which is ineffective against nausea and vomiting when administered alone, but effective against nausea and vomiting when administered in combination with said netupitant, wherein said second dose comprises from 40 to 60% of a minimum effective dose when administered alone.
- 19) (CANCELED)
- 20) (CANCELED)

- 21) (PREVIOUSLY PRESENTED) The method of claim 16 wherein: a) only one dose of netupitant is administered during said five days on day one, comprising about 300 mg. of netupitant as the free base; and b) administering about 12 mg. of dexamethasone on day one; and c) if said patient is undergoing highly emetogenic chemotherapy, administering about 8 mg. of dexamethasone on days two, three and four.
- 22) (CANCELED)
- 23) (PREVIOUSLY PRESENTED) The method of claim 16 wherein said nausea and vomiting is chemotherapy induced nausea and vomiting ("CINV"), radiation therapy induced nausea and vomiting ("RINV"), or post-operative nausea and vomiting ("PONV").
- 24) (PREVIOUSLY PRESENTED) The method of claim 16 wherein said nausea and vomiting is induced by moderately or highly emetogenic chemotherapy.
- 25) (PREVIOUSLY PRESENTED) The method of claim 16 comprising administering moderately or highly emetogenic chemotherapy within from about one hour to about two hours of said administration of said netupitant or pharmaceutically acceptable salt thereof.
- 26) (PREVIOUSLY PRESENTED) The method of claim 16 comprising treating nausea and vomiting in response to highly emetogenic chemotherapy during the acute phase, or in response to highly emetogenic chemotherapy during the delayed phase, or in response to moderately emetogenic chemotherapy during the acute phase, or in response to moderately emetogenic chemotherapy during the delayed phase.
- 27) -51) (CANCELED)
- 52) (CURRENTLY AMENDED) The method of claim 16, comprising ~~orally~~ administering from about 200 to about 400 mg of netupitant as the free base.
- 53) (PREVIOUSLY PRESENTED) The method of claim 16, comprising orally administering about 300 mg of netupitant as the free base.
- 54) (PREVIOUSLY PRESENTED) A method of treating nausea and vomiting in response to an emesis-inducing event for a period of five consecutive days in a patient in need thereof, comprising administering to said patient netupitant or a pharmaceutically acceptable salt thereof, in a therapeutically effective amount which is effective to treat nausea and vomiting during the acute and delayed phases of emesis, wherein said therapeutically

effective amount of netupitant or pharmaceutically acceptable salt thereof is administered on day one of said five consecutive days, no further netupitant or pharmaceutically acceptable salt thereof is administered during said five consecutive days, and said single dose of netupitant or pharmaceutically acceptable salt thereof is effective to treat said nausea and vomiting for said five consecutive days.

- 55) (PREVIOUSLY PRESENTED) The method of claim 54, comprising orally administering from about 200 to about 400 mg of netupitant as the free base.
- 56) (PREVIOUSLY PRESENTED) The method of claim 54, comprising orally administering about 300 mg of netupitant as the free base.
- 57) (CANCELLED)
- 58) (CURRENTLY AMENDED) The method of claim 54 57, wherein when said ~~chemotherapy is~~ emesis inducing event comprises highly emetic chemotherapy, and the chemotherapy is selected from the group consisting of carmustine, cisplatin, cyclophosphamide $\geq 1500 \text{ mg/m}^2$, dacarbazine, dactinomycin, mechlorethamine, streptozotocin and combinations thereof.
- 59) (CURRENTLY AMENDED) The method of claim 54 57, wherein when said ~~chemotherapy is~~ emesis inducing event comprises moderately emetic chemotherapy, and the chemotherapy is selected from the group consisting of carboplatin, cyclophosphamide $< 1500 \text{ mg/m}^2$, cytarabine $> 1 \text{ mg/m}^2$, daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, oxaliplatin and combinations thereof.
- 60) (CURRENTLY AMENDED) The method of claim 54 57, wherein said emesis inducing event comprises chemotherapy ~~is~~ selected from the group consisting of carboplatin, cyclophosphamide, cytarabine $> 1 \text{ mg/m}^2$, daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, carmustine, cisplatin, dacarbazine, dactinomycin, mechlorethamine, streptozotocin, oxaliplatin and combinations thereof.
- 61) (CURRENTLY AMENDED) The method of claim 54 57, ~~wherein said~~ for the treatment of CINV is defined as no emetic episodes and no use of rescue medication following said chemotherapy.
- 62) (CANCELLED)

- 63) (CANCELLED)
- 64) (CURRENTLY AMENDED) The method of claim 61 ~~63~~, wherein said netupitant occupies at least 70% of said patient's striatum NK1 receptors ninety-six hours after said administration.
- 65) (CANCELLED)
- 66) (CANCELLED)
- 67) (CURRENTLY AMENDED) The method of claim 54 ~~63~~, wherein said emesis inducing event ~~chemotherapy~~ is highly emetogenic chemotherapy, and said regimen is effective to prevent or reduce the severity of nausea during the acute and delayed phases.
- 68) (CURRENTLY AMENDED) The method of claim 54 ~~63~~, wherein said emesis inducing event ~~chemotherapy~~ is moderately emetogenic chemotherapy, and said regimen is effective to prevent or reduce the severity of nausea during the acute and delayed phases.
- 69) (CURRENTLY AMENDED) The method of claim 54 ~~63~~, wherein said emesis inducing event ~~chemotherapy~~ comprises cisplatin.
- 70) (CURRENTLY AMENDED) The method of claim 54 ~~63~~, wherein said emesis inducing event ~~chemotherapy~~ comprises carboplatin, cisplatin, oxaliplatin, or doxorubicin.
- 71) (CURRENTLY AMENDED) The method of claim 54 ~~63~~, wherein said emesis inducing event ~~chemotherapy~~ comprises cyclophosphamide.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875				Application or Docket Number 15/003,327		Filing Date 01/21/2016		☐ To be Mailed	
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ENTITY: ☒ **LARGE** ☐ **SMALL** ☐ **MICRO**

APPLICATION AS FILED – PART I

FOR	NUMBER FILED (Column 1)	NUMBER EXTRA (Column 2)	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	(Column 1)	(Column 2)	(Column 3)	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)	ADDITIONAL FEE (\$)
	06/13/2017	CLAIMS REMAINING AFTER AMENDMENT					
	Total (37 CFR 1.16(i))	* 23	Minus	** 28	= 0	X \$80 =	0
	Independent (37 CFR 1.16(h))	* 2	Minus	*** 3	= 0	X \$420 =	0
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
TOTAL ADD'L FEE						0	

AMENDMENT	(Column 1)	(Column 2)	(Column 3)	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)	ADDITIONAL FEE (\$)
		CLAIMS REMAINING AFTER AMENDMENT					
	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".

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LIE
DORRETTA BROOKS

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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

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

Docket Number (Optional)

HHC002US6/CO001

In re Application of: TRENTO et al.

Application No.: 15/003,327

Filed: 01-21-2016

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

The applicant, Helsinn Healthcare SA, owner of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of **prior patent** No. 8623826 as the term of said **prior patent** is presently shortened by any terminal disclaimer. The applicant hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the **prior patent** are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

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expires for failure to pay a maintenance fee;

is held unenforceable;

is found invalid by a court of competent jurisdiction;

is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321;

has all claims canceled by a reexamination certificate;

is reissued; or

is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

Check either box 1 or 2 below, if appropriate.

1. ☐ The undersigned is the applicant. If the applicant is an assignee, the undersigned is authorized to act on behalf of the assignee.

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

2. ☒ The undersigned is an attorney or agent of record. Reg. No. 36942

/Clark G. Sullivan/

Signature

6-14-2017

Date

Clark G. Sullivan

Typed or printed name

Attorney for Applicant

Title

404-483-9360

Telephone Number

- ☒ Terminal disclaimer fee under 37 CFR 1.20(d) included.

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REJECTION OVER A "PRIOR" PATENT**

Docket Number (Optional)

HHC002US6/CO001

In re Application of: TRENTO et al.

Application No.: 15/003,327

Filed: 01-21-2016

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

The applicant, Helsinn Healthcare SA, owner of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of **prior patent** No. 9271975 as the term of said **prior patent** is presently shortened by any terminal disclaimer. The applicant hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the **prior patent** are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

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/Clark G. Sullivan/

Signature

6-14-2017

Date

Clark G. Sullivan

Typed or printed name

Attorney for Applicant

Title

404-483-9360

Telephone Number

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Electronic Patent Application Fee Transmittal				
Application Number:		15003327		
Filing Date:		21-Jan-2016		
Title of Invention:		COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING		
First Named Inventor/Applicant Name:		Fabio TRENTO		
Filer:		Clark G. Sullivan		
Attorney Docket Number:		HHC002US6/CO001		
Filed as Large Entity				
Filing Fees for Utility under 35 USC 111(a)				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Miscellaneous:				
STATUTORY OR TERMINAL DISCLAIMER	1814	1	160	160
Total in USD (\$)				160

Electronic Acknowledgement Receipt

EFS ID:	29490466
Application Number:	15003327
International Application Number:	
Confirmation Number:	1097
Title of Invention:	COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING
First Named Inventor/Applicant Name:	Fabio TRENTO
Customer Number:	140619
Filer:	Clark G. Sullivan
Filer Authorized By:	
Attorney Docket Number:	HHC002US6/CO001
Receipt Date:	14-JUN-2017
Filing Date:	21-JAN-2016
Time Stamp:	10:49:32
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	\$ 160
RAM confirmation Number	061417INTEFSW10501900
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File Listing:					
Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Terminal Disclaimer Filed	HHC002US6_TD1.pdf	143310	no	2
			e3d985c109e0e60f8c17c2990d3836d51e942afe		
Warnings:					
Information:					
2	Terminal Disclaimer Filed	HHC002US6_TD2.pdf	143288	no	2
			da4893dce50d72258167eb5f7cd3996cb097e53b		
Warnings:					
Information:					
3	Terminal Disclaimer Filed	HHC002US6_TD3.pdf	143314	no	2
			72efc0702c6d8df293c85241a2b2fd3ec51c3a03		
Warnings:					
Information:					
4	Fee Worksheet (SB06)	fee-info.pdf	30389	no	2
			6dcca1017fc1b97008af283d47424afb45386bbc		
Warnings:					
Information:					
Total Files Size (in bytes):			460301		

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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.

**TERMINAL DISCLAIMER TO OBIATE A DOUBLE PATENTING
REJECTION OVER A "PRIOR" PATENT**

Docket Number (Optional)

HHC002US6/CO001

In re Application of: TRENTO et al.

Application No.: 15/003,327

Filed: 01-21-2016

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

The applicant, Helsinn Healthcare SA, owner of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of **prior patent** No. 9186357 as the term of said **prior patent** is presently shortened by any terminal disclaimer. The applicant hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the **prior patent** are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

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/Clark G. Sullivan/

Signature

6-14-2017

Date

Clark G. Sullivan

Typed or printed name

Attorney for Applicant

Title

404-483-9360

Telephone Number

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Application Number 	Application/Control No. 15/003,327	Applicant(s)/Patent under Reexamination TRENTO ET AL.	

Document Code - DISQ	Internal Document – DO NOT MAIL
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TERMINAL DISCLAIMER	☒ APPROVED	☐ DISAPPROVED
Date Filed : 6/14/17	This patent is subject to a Terminal Disclaimer	

Approved/Disapproved by:
Lawana Hixon

Application Number 	Application/Control No. 15/003,327	Applicant(s)/Patent under Reexamination TRENTO ET AL.	
Document Code - DISQ		Internal Document – DO NOT MAIL	

TERMINAL DISCLAIMER	☐ APPROVED	☒ DISAPPROVED
Date Filed : 6/14/17	This patent is subject to a Terminal Disclaimer	

Approved/Disapproved by:
2/Tds both disapproved (PP: 9271975, and 9186357). Td fee not paid and no authorization to charged deposit account, see FP 14.24 and 14.26.07. Please re-submit tds and pay fees. Lawana Hixon

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In re Application of: TRENTO et al.

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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.

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.
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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.

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

Docket Number (Optional)

HHC002US6/CO001

In re Application of: TRENTO et al.

Application No.: 15/003,327

Filed: 01-21-2016

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

The applicant, Helsinn Healthcare SA, owner of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of **prior patent** No. 9271975 as the term of said **prior patent** is presently shortened by any terminal disclaimer. The applicant hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the **prior patent** are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the applicant does not disclaim the terminal part of the term of any patent granted on the instant application that would extend to the expiration date of the full statutory term of the **prior patent**, "as the term of said **prior patent** is presently shortened by any terminal disclaimer," in the event that said **prior patent** later:

- expires for failure to pay a maintenance fee;
- is held unenforceable;
- is found invalid by a court of competent jurisdiction;
- is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321;
- has all claims canceled by a reexamination certificate;
- is reissued; or
- is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

Check either box 1 or 2 below, if appropriate.

1. ☐ The undersigned is the applicant. If the applicant is an assignee, the undersigned is authorized to act on behalf of the assignee.

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

2. ☒ The undersigned is an attorney or agent of record. Reg. No. 36942

/Clark G. Sullivan/6/16/2017

Signature

Date

Clark G. Sullivan

Typed or printed name

Attorney for Applicant

Title

404-483-9360

Telephone Number

- ☒ Terminal disclaimer fee under 37 CFR 1.20(d) included.

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.

This collection of information is required by 37 CFR 1.321. 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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Electronic Patent Application Fee Transmittal

Application Number:	15003327			
Filing Date:	21-Jan-2016			
Title of Invention:	COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING			
First Named Inventor/Applicant Name:	Fabio TRENTO			
Filer:	Clark G. Sullivan			
Attorney Docket Number:	HHC002US6/CO001			
Filed as Large Entity				
Filing Fees for Utility under 35 USC 111(a)				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Miscellaneous:				
STATUTORY OR TERMINAL DISCLAIMER	1814	2	160	320
Total in USD (\$)				320

Electronic Acknowledgement Receipt

EFS ID:	29522788
Application Number:	15003327
International Application Number:	
Confirmation Number:	1097
Title of Invention:	COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING
First Named Inventor/Applicant Name:	Fabio TRENTO
Customer Number:	140619
Filer:	Clark G. Sullivan
Filer Authorized By:	
Attorney Docket Number:	HHC002US6/CO001
Receipt Date:	16-JUN-2017
Filing Date:	21-JAN-2016
Time Stamp:	17:47:35
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	\$320
RAM confirmation Number	061917INTEFSW17481800
Deposit Account	
Authorized User	

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

File Listing:					
Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Terminal Disclaimer Filed	HHC002US6_TD2_NEW.pdf	153556	no	2
			6c2bf139841f6b31f3caa6949baf48680a36d9e0		
Warnings:					
Information:					
2	Terminal Disclaimer Filed	HHC002US6_TD3_NEW.pdf	143337	no	2
			5865c08a18055a2702d7a057eebccb7f158975cd		
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	30346	no	2
			7efe95e500304d1a3c2c773f9aafa119b23aff232		
Warnings:					
Information:					
Total Files Size (in bytes):			327239		
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.					

Application Number 	Application/Control No. 15/003,327	Applicant(s)/Patent under Reexamination TRENTO ET AL.	

Document Code - DISQ	Internal Document – DO NOT MAIL
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TERMINAL DISCLAIMER	☒ APPROVED	☐ DISAPPROVED
Date Filed : 16 June, 2017	This patent is subject to a Terminal Disclaimer	

Approved/Disapproved by: <u>/CRYSTAL QUEEN/</u> Technology Center: <u>PLRC</u> Telephone: <u>2 TDS APPROVED</u>
--



UNITED STATES PATENT AND TRADEMARK OFFICE

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

NOTICE OF ALLOWANCE AND FEE(S) DUE

140619 7590 09/08/2017
Sullivan IP Solutions, LLC
PO Box 2252
New York, NY 10163

EXAMINER

WEBB, WALTER E

ART UNIT

PAPER NUMBER

1612

DATE MAILED: 09/08/2017

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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15/003,327

01/21/2016

Fabio TRENTA

HHC002US6/CO001

1097

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	UNDISCOUNTED	\$960	\$0	\$0	\$960	12/08/2017

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)

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.

140619 7590 09/08/2017
Sullivan IP Solutions, LLC
PO Box 2252
New York, NY 10163

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.
15/003,327	01/21/2016	Fabio TRENTO	HHC002US6/CO001	1097

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	UNDISCOUNTED	\$960	\$0	\$0	\$960	12/08/2017

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, 1 _____ (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. 2 _____ 3 _____
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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 credits any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).
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5. Change in Entity Status (from status indicated above)

- ☐ Applicant certifying micro entity status. See 37 CFR 1.29
- ☐ Applicant asserting small entity status. See 37 CFR 1.27
- ☐ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

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.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____



UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/003,327	01/21/2016	Fabio TRENTA	HHC002US6/CO001	1097
140619	7590	09/08/2017	EXAMINER	
Sullivan IP Solutions, LLC PO Box 2252 New York, NY 10163			WEBB, WALTER E	
			ART UNIT	PAPER NUMBER
			1612	
DATE MAILED: 09/08/2017				

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b) (Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 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.

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6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
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. 15/003,327	Applicant(s) TRENTO ET AL.	
	Examiner WALTER WEBB	Art Unit 1612	AIA (First Inventor to File) Status No

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

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 communications filed 6/14/17 and 6/16/2017.
☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are 16-18,21,23-26,52-56,58-61,64 and 67-71. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

- a) ☐ All b) ☐ Some *c) ☐ None of the:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

* Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.

THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.
Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

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

/WALTER WEBB/
Primary Examiner, Art Unit 1612

Comment: Election/Restrictions

Claim 54 is allowable. The restriction requirement among as set forth in the Office action mailed on 3/13/2017 has been reconsidered in view of the allowability of claims to the elected invention pursuant to MPEP § 821.04(a). **The restriction requirement is hereby withdrawn as to any claim that requires all the limitations of an allowable claim.**

In view of the above noted withdrawal of the restriction requirement, applicant is advised that if any claim presented in a continuation or divisional application is anticipated by, or includes all the limitations of, a claim that is allowable in the present application, such claim may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application.

Once a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. See *In re Ziegler*, 443 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

Correspondence

Art Unit: 1612

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

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

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

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

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

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
A61K	31/434	9/1/2017	WW

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

CPC					
Symbol				Type	Version
A61K	31	/	496	F	2013-01-01
A61K	9	/	4808	I	2013-01-01
A61K	31	/	4178	I	2013-01-01
A61K	31	/	473	I	2013-01-01
A61K	31	/	573	I	2013-01-01
A61K	45	/	06	I	2013-01-01
A61K	9	/	2054	I	2013-01-01
A61K	9	/	4858	I	2013-01-01
A61K	9	/	0053	I	2013-01-01
Y10S	514	/	872	A	2013-01-01
		/			
		/			
		/			
		/			
		/			

CPC Combination Sets								
Symbol				Type	Set	Ranking	Version	
A61K		31	/	4178	I	1	1	2013-01-01
A61K		2300	/	00	A	1	2	2013-01-01
A61K		31	/	473	I	2	1	2013-01-01
A61K		2300	/	00	A	2	2	2013-01-01
A61K		31	/	496	I	3	1	2013-01-01
A61K		2300	/	00	A	3	2	2013-01-01
A61K		31	/	573	I	4	1	2013-01-01
A61K		2300	/	00	A	4	2	2013-01-01

NONE		Total Claims Allowed: 23	
(Assistant Examiner)	(Date)		
/WALTER WEBB/ Primary Examiner.Art Unit 1612 (Primary Examiner)	09/01/2017 (Date)	O.G. Print Claim(s) Claim 1	O.G. Print Figure None

Issue Classification 	Application/Control No. 15003327	Applicant(s)/Patent Under Reexamination TRENTO ET AL.
	Examiner WALTER WEBB	Art Unit 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	16	17	61												
2	17	18	64												
3	18	19	67												
4	21	20	68												
5	23	21	69												
6	24	22	70												
7	25	23	71												
8	26														
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10	53														
11	54														
12	55														
13	56														
14	58														
15	59														
16	60														

NONE	Total Claims Allowed: 23	
(Assistant Examiner)	(Date)	
/WALTER WEBB/ Primary Examiner.Art Unit 1612	09/01/2017	O.G. Print Claim(s) Claim 1
(Primary Examiner)	(Date)	O.G. Print Figure None



UNITED STATES PATENT AND TRADEMARK OFFICE

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

BIB DATA SHEET

CONFIRMATION NO. 1097

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.		
15/003,327	01/21/2016	514	1612	HHC002US6/CO001		
RULE						
APPLICANTS Helsinn Healthcare SA, Lugano/Pazzallo, SWITZERLAND;						
INVENTORS Fabio TRENTO, Pare, ITALY; Sergio CANTOREGGI, Cagiallo, SWITZERLAND; Giorgia ROSSI, Cernobbio, ITALY; Roberta CANNELLA, Varese, ITALY; Daniele BONADEO, Casalzuigno, ITALY;						
** CONTINUING DATA ***** This application is a CON of 14/069,970 11/01/2013 PAT 9271975 which is a CON of 13/077,462 03/31/2011 PAT 8623826 which is a CON of PCT/IB2010/003106 11/18/2010 which claims benefit of 61/262,470 11/18/2009 and claims benefit of 61/382,709 09/14/2010						
** FOREIGN APPLICATIONS *****						
** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ** 02/05/2016						
Foreign Priority claimed	☐ Yes ☒ No	☐ Met after Allowance	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
35 USC 119(a-d) conditions met	☐ Yes ☒ No	Initials	ITALY	5	13	2
Verified and Acknowledged	/WALTER E WEBB/ Examiner's Signature					
ADDRESS Sullivan IP Solutions, LLC PO Box 2252 New York, NY 10163 UNITED STATES						
TITLE COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING						
FILING FEE RECEIVED 2240	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	80752	emesis or nausea or vomit or vomiting or chemotherapy	USPAT	OR	ON	2017/09/01 12:47
L2	28	l1 and netupitant	USPAT	OR	ON	2017/09/01 12:48
L3	27	l2 and day	USPAT	OR	ON	2017/09/01 12:49

9/ 1/ 2017 12:53:28 PM
C:\ Users\ wwbb\ Documents\ EAST\ Workspaces\ 15003327_Netupitant for Centrally Mediated Nausea and Vomiting.wsp

<i>Index of Claims</i> 	Application/Control No. 15003327	Applicant(s)/Patent Under Reexamination TRENTO ET AL.
	Examiner WALTER WEBB	Art Unit 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	03/10/2016	09/01/2016	03/13/2017	09/01/2017						
	1	-	-	-	-						
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	3	-	-	-	-						
	4	-	-	-	-						
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	8	-	-	-	-						
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	13	-	-	-	-						
	14	-	-	-	-						
	15	-	-	-	-						
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2	17	✓	✓	✓	=						
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	20	-	-	-	-						
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	22	-	-	-	-						
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6	24	✓	✓	✓	=						
7	25	✓	✓	✓	=						
8	26	✓	✓	✓	=						
	27	-	-	-	-						
	28	-	-	-	-						
	29	-	-	-	-						
	30	-	-	-	-						
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	32	-	-	-	-						
	33	-	-	-	-						
	34	-	-	-	-						
	35	-	-	-	-						
	36	-	-	-	-						

<i>Index of Claims</i> 	Application/Control No. 15003327	Applicant(s)/Patent Under Reexamination TRENTO ET AL.
	Examiner WALTER WEBB	Art Unit 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	03/10/2016	09/01/2016	03/13/2017	09/01/2017						
	37	-	-	-	-						
	38	-	-	-	-						
	39	-	-	-	-						
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	42	-	-	-	-						
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	47	-	-	-	-						
	48	-	-	-	-						
	49	-	-	-	-						
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	51	-	-	-	-						
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10	53	✓	✓	✓	=						
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13	56	✓	✓	✓	=						
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	66			N	-						
19	67			N	=						
20	68			N	=						
21	69			N	=						
22	70			N	=						
23	71			N	=						

REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL (Submitted Only via EFS-Web)

Application Number	15003327	Filing Date	2016-01-21	Docket Number (if applicable)	HHC002US6/CO001	Art Unit	1612
First Named Inventor	Fabio TRENTO et al.			Examiner Name	WALTER E. WEBB		

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.

Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. The Instruction Sheet for this form is located at WWW.USPTO.GOV

SUBMISSION REQUIRED UNDER 37 CFR 1.114

Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____

☐ Other _____

☒ Enclosed

☐ Amendment/Reply

☒ Information Disclosure Statement (IDS)

☐ Affidavit(s)/ Declaration(s)

☐ Other _____

MISCELLANEOUS

☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of months _____
(Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

☐ Other _____

FEES

☒ The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.
The Director is hereby authorized to charge any underpayment of fees, or credit any overpayments, to
Deposit Account No 600254

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

☒ Patent Practitioner Signature

Applicant Signature

Signature of Registered U.S. Patent Practitioner			
Signature	Clark G. Sullivan/	Date (YYYY-MM-DD)	2017-11-21
Name	Clark G. Sullivan	Registration Number	36942

This collection of information is required by 37 CFR 1.114. 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.

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

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

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

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
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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 Patent Application Fee Transmittal				
Application Number:		15003327		
Filing Date:		21-Jan-2016		
Title of Invention:		COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING		
First Named Inventor/Applicant Name:		Fabio TRENTO		
Filer:		Clark G. Sullivan		
Attorney Docket Number:		HHC002US6/CO001		
Filed as Large Entity				
Filing Fees for Utility under 35 USC 111(a)				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Miscellaneous:				
RCE- 2ND AND SUBSEQUENT REQUEST	1820	1	1700	1700
Total in USD (\$)				1700

Electronic Acknowledgement Receipt

EFS ID:	31007222
Application Number:	15003327
International Application Number:	
Confirmation Number:	1097
Title of Invention:	COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING
First Named Inventor/Applicant Name:	Fabio TRENTO
Customer Number:	140619
Filer:	Clark G. Sullivan
Filer Authorized By:	
Attorney Docket Number:	HHC002US6/CO001
Receipt Date:	21-NOV-2017
Filing Date:	21-JAN-2016
Time Stamp:	17:48:27
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	\$ 1700
RAM confirmation Number	112217INTEFSW17485400
Deposit Account	
Authorized User	

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

File Listing:					
Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Non Patent Literature	D9_Advances_drug_discovery.pdf	497843	no	4
			47fa19c021db0dfc49454a35da13ca4f88d18a57		
Warnings:					
Information:					
2	Non Patent Literature	D10_Antiemetics_MASCC_guidelines.pdf	2840784	no	12
			dda6a95b9c7478d8acd12ba38e35e4d8cee41589		
Warnings:					
Information:					
3	Non Patent Literature	D11_Management_postoperative_nausea_vomiting.pdf	170317	no	1
			47af97379798a40eb72420a29ab911219d5b06d2		
Warnings:					
Information:					
4	Non Patent Literature	D12_Palonosetron_anti-emetic_anti-nausea.pdf	2262742	no	12
			bd054f83be329ae62aea119eb0969b9e692cf950		
Warnings:					
Information:					
5	Non Patent Literature	D13_Palonosetron_Prevention.pdf	3251678	no	22
			40885d5e5b2e767ced85b3aad15aa6f11313e8f4		
Warnings:					
Information:					
6	Non Patent Literature	D14_IPER_WO2011061622.pdf	734478	no	9
			2717a658d41961da5629cb8eb6e67f23c58a1442		
Warnings:					
Information:					

7	Non Patent Literature	D15-Jordan.pdf	1638061	no	8
			a021bf3424b68045377eef6895e55b1bb1676838		
Warnings:					
Information:					
8	Non Patent Literature	D16_EMEA_Guidelines_Pharmaceutical.pdf	714537	no	8
			459a5c96acec65120c5854e03a66e0b7a0d7f1a1		
Warnings:					
Information:					
9	Non Patent Literature	D17_Rizzi_A_et_al.pdf	1054203	no	12
			7690753ee5206938aa2e220fe6ec02492c824dfb		
Warnings:					
Information:					
10	Non Patent Literature	D18_Non-exhaustive_list_NK-1_antagonist.pdf	482602	no	5
			2da6b8ac5aeb51df30af98100be2630db533ca02		
Warnings:					
Information:					
11	Non Patent Literature	D19_Clinical_study_report_Net_u_08-18.pdf	483405	no	6
			ee7824d5e642f50bceb81731505e804e0a6a9e97		
Warnings:					
Information:					
12	Non Patent Literature	D20_Clinical_study_report_Palo_10-01.pdf	185384	no	3
			97327107ef8d40217d32bb5c8e13716d91d7715e		
Warnings:					
Information:					
13	Other Reference-Patent/App/Search documents	EP_Decision_rejecting-the-opposition.pdf	768280	no	10
			a056b8962221559c5cbcd830a9966f796e99706e		
Warnings:					
Information:					

14	Information Disclosure Statement (IDS) Form (SB08)	US6_IDS_SB08.pdf	613303	no	5
			ddfd80bb33baaf10dad9dadf5b041b9c57ddcdaf7		
Warnings:					
Information:					
15	Transmittal Letter	US6_IDS_Transmittal.pdf	50322	no	1
			543265b98f646aaebeceb5ac500fe162079e479c		
Warnings:					
Information:					
16	Foreign Reference	WO2004067005.pdf	2384438	no	27
			860de1dc976396aa39097487b9edcb74d6b56d79		
Warnings:					
Information:					
17	Foreign Reference	WO2004073714.pdf	4087644	no	39
			7ef87881c738011c71910c4c60057ad2834653e4		
Warnings:					
Information:					
18	Foreign Reference	WO2008049552.pdf	3413123	no	36
			5970bf6093800ff6aa9132aadf891c06d6c53af7		
Warnings:					
Information:					
19	Request for Continued Examination (RCE)	US6_RCE.pdf	697606	no	3
			e8fb9e14fdc60da8f688990c958368995965bb2d		
Warnings:					
Information:					
20	Fee Worksheet (SB06)	fee-info.pdf	30451	no	2
			e13c0f43f2cbd170652020f357dd71a30568df10		
Warnings:					
Information:					
Total Files Size (in bytes):			26361201		

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

New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44bis)

Applicant's or agent's file reference 23278.20	FOR FURTHER ACTION	See item 4 below
International application No. PCT/IB2010/003106	International filing date (<i>day/month/year</i>) 18 November 2010 (18.11.2010)	Priority date (<i>day/month/year</i>) 18 November 2009 (18.11.2009)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant HELSINN HEALTHCARE SA		

1.	This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 bis.1(a).																								
2.	This REPORT consists of a total of 9 sheets, including this cover sheet. In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.																								
3.	This report contains indications relating to the following items: <table style="width: 100%; border: none;"> <tr> <td style="width: 5%; text-align: center;">☒</td> <td style="width: 25%;">Box No. I</td> <td>Basis of the report</td> </tr> <tr> <td style="text-align: center;">☐</td> <td>Box No. II</td> <td>Priority</td> </tr> <tr> <td style="text-align: center;">☒</td> <td>Box No. III</td> <td>Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</td> </tr> <tr> <td style="text-align: center;">☐</td> <td>Box No. IV</td> <td>Lack of unity of invention</td> </tr> <tr> <td style="text-align: center;">☒</td> <td>Box No. V</td> <td>Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</td> </tr> <tr> <td style="text-align: center;">☐</td> <td>Box No. VI</td> <td>Certain documents cited</td> </tr> <tr> <td style="text-align: center;">☐</td> <td>Box No. VII</td> <td>Certain defects in the international application</td> </tr> <tr> <td style="text-align: center;">☒</td> <td>Box No. VIII</td> <td>Certain observations on the international application</td> </tr> </table>	☒	Box No. I	Basis of the report	☐	Box No. II	Priority	☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability	☐	Box No. IV	Lack of unity of invention	☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement	☐	Box No. VI	Certain documents cited	☐	Box No. VII	Certain defects in the international application	☒	Box No. VIII	Certain observations on the international application
☒	Box No. I	Basis of the report																							
☐	Box No. II	Priority																							
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability																							
☐	Box No. IV	Lack of unity of invention																							
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement																							
☐	Box No. VI	Certain documents cited																							
☐	Box No. VII	Certain defects in the international application																							
☒	Box No. VIII	Certain observations on the international application																							
4.	The International Bureau will communicate this report to designated Offices in accordance with Rules 44bis.3(c) and 93bis.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44bis .2).																								

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Date of issuance of this report 22 May 2012 (22.05.2012) Authorized officer Cécile Chatel e-mail: ro.ib@wipo.int
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PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

To:

see form PCT/ISA/220

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/B2010/003106

International filing date (day/month/year)
18.11.2010

Priority date (day/month/year)
18.11.2009

International Patent Classification (IPC) or both national classification and IPC
INV. A61K31/4178 A61K31/473 A61K31/496 A61K31/573 A61K45/06 A61P1/08

Applicant
HELSINN HEALTHCARE S.A.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office
P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk - Pays Bas
Tel. +31 70 340 - 2040
Fax: +31 70 340 - 3016

Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

Opravz, Petra

Telephone No. +31 70 340-2694



Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))
3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:
 - a. (means)
 - ☐ on paper
 - ☐ in electronic form
 - b. (time)
 - ☐ in the international application as filed
 - ☐ together with the international application in electronic form
 - ☐ subsequently to this Authority for the purposes of search
4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 34, 42(all partially)

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international search (*specify*):

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):

☒ no international search report has been established for the whole application or for said claims Nos. 34, 42(all partially)

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13~~ter~~.1(a) or (b).

☐ See Supplemental Box for further details

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	<u>1-15, 18-22, 25-33, 35-41, 43-51(completely); 34, 42(partially)</u>
	No: Claims	<u>16, 17, 23, 24</u>
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-33, 35-41, 43-51(completely); 34, 42(partially)</u>
Industrial applicability (IA)	Yes: Claims	<u>1-33, 35-41, 43-51(completely); 34, 42(partially)</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 34 and 42 encompass a large number of compounds which are defined only by reference to a desired functional activity (compound being a "prodrug"). This functional term does not give a specific technical guidance for the selection of the suitable derivatives, without proven general knowledge, to show which derivatives are suitable "prodrugs" in the particular case of the current problem and thus could be seen as a mere invitation to the skilled person to perform a research program in order to find suitable variants.

The description does not provide support and disclosure within the meaning of Article 6 PCT and, in addition, does not appear to be sufficiently disclosed under Article 5 PCT for any of such compounds having the desired function and there is no general common knowledge of this kind available to the skilled person.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognise as patentable claims to the use of a compound in medical treatment (claims 1-33, 50 and 51 of the present application), but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment.

Patentability, in particular novelty and inventive step, of claims 1-33, 50 and 51 has been assessed on the basis of a purpose-limited product claim taking into account the alleged effects of the substance or composition.

Reference is made to the following documents:

- D1 REDDY G KESAVA ET AL: "Novel neurokinin-1 antagonists as antiemetics for the treatment of chemotherapy-induced emesis.", SUPPORTIVE CANCER THERAPY 1 APR 2006 LNKD- PUBMED: 18632487, vol. 3, no. 3, 1 April 2006 (2006-04-01), pages 140-142, XP002626039, ISSN: 1543-2912

- D2 DIEMUNSCH P ET AL: "Neurokinin-1 receptor antagonists in the prevention of postoperative nausea and vomiting.", BRITISH JOURNAL OF ANAESTHESIA JUL 2009 LNKD- PUBMED:19454547, vol. 103, no. 1, July 2009 (2009-07), pages 7-13, XP002626040, ISSN: 1471-6771
- D3 WO 2008/049552 A1 (HELSINN HEALTHCARE SA [CH]; BONADEO DANIELE [IT]; CALDERARI GIORGIO [C] 2 May 2008 (2008-05-02)
- D4 DE WIT R: "Current position of 5HT3 antagonists and the additional value of NK1 antagonists; a new class of antiemetics.", BRITISH JOURNAL OF CANCER 16 JUN 2003 LNKD- PUBMED:12799621, vol. 88, no. 12, 16 June 2003 (2003-06-16), pages 1823-1827, XP002626041, ISSN: 0007-0920
- D5 GRUNBERG STEVEN M ET AL: "Effectiveness of a single-day three-drug regimen of dexamethasone, palonosetron, and aprepitant for the prevention of acute and delayed nausea and vomiting caused by moderately emetogenic chemotherapy.", SUPPORTIVE CARE IN CANCER : OFFICIAL JOURNAL OF THE MULTINATIONAL ASSOCIATION OF SUPPORTIVE CARE IN CANCER MAY 2009 LNKD- PUBMED:19037667, vol. 17, no. 5, May 2009 (2009-05), pages 589-594, XP002626042, ISSN: 1433-7339

Unless otherwise mentioned, the passages cited in the search report are considered to represent the pertinent passages of said documents.

Novelty (Article 33(2) PCT)

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 16, 17, 23 and 24 is not new in the sense of Article 33(2) PCT.

D1 discloses a NK-1 receptor antagonist netupitant as a potential agent for the treatment of chemotherapy-induced nausea and vomiting when administered orally (page 140, "Abstract"; page 141, Table 1, phase II study as in the present application: see page 23).

Thus, D1 anticipates the subject-matter of claims 16, 17, 23 and 24.

Inventive step (Article 33(3) PCT)

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-15, 18-22, 25-51 does not involve an inventive step in the sense of Article 33(3) PCT.

D2, which is considered to represent the closest prior art, discloses a combination of NK-1 receptor antagonist casopitant, 5-HT₃ receptor antagonist ondansetron and dexamethasone, which reduces cancer-chemotherapy-induced nausea and vomiting (page 10, left col.).

The present claims 1, 3-5, 9, 10, 19 and 32 differ from D2 in that NK-1 receptor antagonist is netupitant.

The effect of this difference is not known.

Consequently, the objective technical problem to be solved by the present application is defined as a provision of an alternative cancer-chemotherapy-induced nausea and vomiting treatment.

The solution provided is considered to be obvious for the following reason:

D1 discloses NK-1 receptor antagonist netupitant as a potential agent for the treatment of chemotherapy-induced nausea and vomiting when administered orally (page 140, "Abstract"; page 141, Table 1, phase II study as in the present application: see page 23). When combining D1 with D2, a skilled person would arrive at the presently claimed solution by using an alternative NK-1 receptor antagonist, i.e. netupitant (D1), in a combination with ondansetron and dexamethasone in order to treat cancer-chemotherapy-induced nausea and vomiting (D2).

Thus, claims 1, 3-5, 9, 10, 19 and 32 lack an inventive step (Article 33(3) PCT).

Furthermore, the use of NK-1 receptor antagonists with either dexamethasone or 5-HT₃ receptor antagonists alone, or with a 5HT₃ receptor antagonist plus dexamethasone, is known in the prior art (D2: page 9, right col.; D4, D5: "Abstract").

Furthermore, each of the compounds presently claimed in combination as a treatment of nausea and vomiting is separately known to possess a therapeutic activity against the same disease or condition (see D1: page 140, "Abstract", "Rationale"; page 141, Table 1; D3: page 11; page 16, lines 20-27; D4: "Abstract"; D5: page 590, 4th par.). 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 for nausea and vomiting.

Therefore, a skilled person would add any of the claimed compounds of the present claims 18, 27, 34 and 42 which are known to treat chemotherapy-induced nausea and vomiting (D1-D5), in order to solve the problem posed as he/she would expect at least an additive effect from combining the claimed compounds. Therefore, a skilled person would arrive at the solution provided.

Hence, in the absence of a surprising effect resulting from that combination, the subject-matter of claims 18, 27, 34 and 42 does not involve an inventive step (Article 33 (3) PCT).

The features claimed in the dependent claims 2, 6-8, 11-15, 20-22, 25, 26, 28-31, 33, 35-41, 43-51 refer to matters of common practice to a skilled person; as such, they represent mere obvious alternative embodiments to the composition/therapy in question. In the absence of any indication as to a (further) technical effect being obtained by these features, the claims concerned lack an inventive step. In particular it is obvious to optimize routes of administration, pharmaceutical formulations, dosages and dosage regimens in an obvious composition, unless the applicant provides support for attributing a (further) technical effect thereof.

Moreover, determination of the best individual treatment schedule, in particular the prescribing and modification of drug dosage regimens used for administering a particular medicament, so as to comply with the specific needs of a patient and to achieve the desired result of the treatment in an individual patient, is a part of the routine practice of a medical practitioner in his professional skill in curing, preventing and alleviating the symptoms of suffering and illness.

Re Item VIII

Certain observations on the international application

1. It is to be noted that the functional feature employed in the present claims 1, 3, 16 and 17, i.e. "occupies at least 70% or 80% of NK1-receptors in the striatum seventy-two hours after said administration", does not limit the scope of the present claims 1, 3, 16 and 17, which are directed to the treatment of nausea and vomiting.

The same applies for the feature "for five consecutive days" in the independent claims 1 and 16, which is considered to be a result to be achieved.

2. There is a typographical error in claim 50, which is dependent on claim 51.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number	15003327
	Filing Date	2016-01-21
	First Named Inventor	Fabio TRENTA
	Art Unit	1612
	Examiner Name	Walter E. Webb
	Attorney Docket Number	HHC002US6/CO001

U.S.PATENTS						Remove
Examiner Initial*	Cite No	Patent Number	Kind Code ¹	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	6297375		2001-10-02	Bos , et al.	
	2	6747026		2004-06-08	Hoffmann, et al.	
	3	6806370		2004-10-19	Hoffmann, et al.	

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	1	2008/049552	WO	A1	2008-05-02	HELSINN HEALTHCARE S.A., et al.		

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	15003327
Filing Date	2016-01-21
First Named Inventor	Fabio TRENT0
Art Unit	1612
Examiner Name	Walter E. Webb
Attorney Docket Number	HHC002US6/CO001

2	2004/073714	WO	A1	2004-09-02	HELSINN HEALTHCARE S.A., et al.		
3	2004/067005	WO	A1	2004-08-12	HELSINN HEALTHCARE S.A., et al.		

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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	Grunberg et al., SUPPORT CANCER CARE (2009) 17:589-594	
	2	Jordan et al., THE ONCOLOGIST, Vol. 12, No. 9, 1143-1150, September 2007	
	3	Goldhill Advances in Drug Discovery 2006	
	4	Herrstedt J Antiemetics: an update and the MASCC guidelines applied in clinical practice; Nature Clin Practice Jan 2008, 5:32-43.	
	5	Muchatuta Ther & Risk Clin Management 2009, 5:21 -34	
	6	Aapro M Ther & Risk Clin Management 2007, 3:1009-1020	
	7	Yang, et al. Adis Drug Evaluation Drugs 2009, 69: 2257-2278	

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	15003327
Filing Date	2016-01-21
First Named Inventor	Fabio TRENTO
Art Unit	1612
Examiner Name	Walter E. Webb
Attorney Docket Number	HHC002US6/CO001

8	PER in respect of PCT/IB2010/003106 (W02011061622); May 22, 2012.
9	Karin, et al.; The Oncologist 2007, 12:1143-1150.
10	EMA "Guideline On Pharmaceutical Fixed Combination Products" 18 Dec 2006.
11	Rizzi, Anna et al., "In vitro and in vivo pharmacological characterization of the novel NK1 receptor selective antagonist Netupitant" 23.06.2012, [cited 23.06.2012] Peptides 37 (2012) 86-97.
12	Non-exhaustive list of fourteen NK-1 antagonist; D18.
13	Clinical study report; NETU-08-18; INVESTIGATIONAL PLAN; June 12, 2013.
14	Clinical study report; Single-dose, multi-center, randomized, double-blind, double-dummy, parallel group study to assess the efficacy and safety of ... PALO-10-01; June 5, 2013.
15	Decision rejecting the opposition (Art. 101(2) EPC) issued in corresponding EP application no. 14151676.5 on September 26, 2017.

If you wish to add additional non-patent literature document citation information please click the Add button

EXAMINER SIGNATURE

Examiner Signature		Date Considered	
--------------------	--	-----------------	--

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

¹ See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. ² Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). ³ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁴ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. ⁵ Applicant is to place a check mark here if English language translation is attached.

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	15003327
Filing Date	2016-01-21
First Named Inventor	Fabio TRENTO
Art Unit	1612
Examiner Name	Walter E. Webb
Attorney Docket Number	HHC002US6/CO001

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)	2017-11-21
Name/Print	Clark G. Sullivan	Registration Number	36942

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In re Patent Application of:	)	
TRENTO et al.	)	Customer No.: 140619
	)	
Application No.: 15/003,327	)	Confirmation No.: 1097
	)	
Filing Date: 01-21-2016	)	Art Unit: 1612
	)	
For: COMPOSITIONS AND METHODS FOR	)	Examiner: Walter E. Webb
TREATING CENTRALLY MEDIATED	)	
NAUSEA AND VOMITING	)	

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Respectfully submitted,

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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
5 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-
10 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-HT₃ (5-
hydroxytryptamine) receptor antagonists has been developed that treat such emesis by
antagonizing cerebral functions associated with the 5-HT₃ receptor. *See Drugs Acting on*
5-Hydroxytryptamine Receptors: The Lancet Sep. 23, 1989 and references cited therein.
15 Drugs within this class include ondansetron, granisetron, alosetron, tropisetron, and
dolasetron. These 5-HT₃ 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
20 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-HT₃ antagonist every day until the risk
of emesis has substantially subsided. The present class of 5-HT₃ antagonists has not
25 proven especially helpful meeting this need, however, because the 5-HT₃ 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*
5HT₃ 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-HT₃ 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-HT₃ receptor antagonists, has a surprising half-life of about 40 hours, and is effective to
5 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 HCl	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.

10

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,
15 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
20 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.

10 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.

15 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-HT₃ receptor antagonist and its pharmaceutically acceptable carriers that would facilitate making a formulation with this increased stability.

20 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.

25 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
5 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 1/10th the amount of other
10 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
15 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)
20 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
25 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

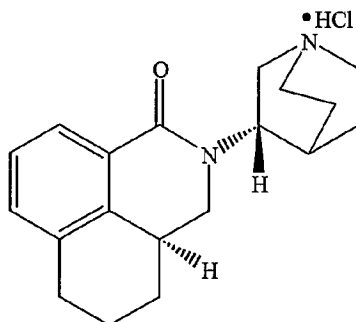
5 DEFINITIONS

“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, 10 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 15 any other element, integer or step, or group of elements, integers or steps

“Palonosetron” means (3a*S*)-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:

20



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.

5 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
10 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
15 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.

20 • 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.

25 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
30 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
5 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
10 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
15 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
20 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
25 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.

5 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
10 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

15 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

20 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 $\pm$ 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.

5

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 $\pm$ 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 studied in concentrations of 5 μ g/mL and 30 μ g/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.

10

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
5 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.
10 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
15 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
5 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
10 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.
- 15 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.
- 20 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.
- 25 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.
- 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.
- 10 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
15 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
20 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
25 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
- 10 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
- 15 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.
- 20 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
- 25 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.
- 5 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 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.
- 15 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
20 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.
- 25 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
- 5 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.
- 10 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.
- 15 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.
- 20 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.
- 25 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
5 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
10 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.
- 15 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
25 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

International 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-HT ₃ 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 --- -/--	

☒ 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
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- *&* document member of the same patent family

Date of the actual completion of the international search

21 April 2004

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/000888

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

national 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

International Application No

PCT/EP2004/000888

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		PL 166267 B1	28-04-1995
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		ZA 9009529 A	26-08-1992

(19) World Intellectual Property
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(43) International Publication Date
2 September 2004 (02.09.2004)

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(10) International Publication Number
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- (21) International Application Number: PCT/EP2004/001558 (81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (22) International Filing Date: 18 February 2004 (18.02.2004)
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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).
- Published:**
— with international search report
- 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.



WO 2004/073714 A1

(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-HT₃ receptor antagonists. In particular, the invention discloses methods for reducing post-operative nausea and vomiting and other emetic events with palonosetron.

METHOD OF TREATING POST-OPERATIVE NAUSEA AND VOMITING

FIELD OF THE INVENTION

5 The present invention discloses methods to treat post-operative nausea and vomiting, as well as emesis generally, with 5-HT₃ receptor antagonists. In particular, the invention discloses methods for reducing post-operative nausea and vomiting and other emetic events with palonosetron.

10 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
15 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,
20 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 nausea and vomiting: its etiology, treatment and prevention." *Anesthesiology*, 77:162-184), however five general types
25 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 gastrointestinal 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-HT₃ (5-hydroxytryptamine) receptor antagonists has been developed that treat emesis by antagonizing cerebral functions associated with the 5-HT₃ 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, GlaxoWellcome), 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-
5 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
10 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
15 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-
20 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)).
25

Kytril (granisetron hydrochloride), a selective blocking agent of the 5-HT₃ 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
5 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.
10 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
15 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-HT₃ receptor and can be useful for the treatment of
20 emesis.

Additional 5HT receptor antagonists have been found. For example, Ponchant et al. (1991) "Synthesis of 5-¹²⁵I-Iodo-Zacopride, A New Probe for 5-HT₃ Receptor Sites," *J. Lab. Cpds. and Radiopharm.*, Vol. XXIX, No. 10, pp. 1147-1155, discloses substituted 3-quinuclidinyl benzamides useful for 5-HT₃ serotonin receptor binding.
25 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-HT₃ 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
5 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-HT₃ 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
10 (Markham, A. & Sorkin, E. M. (1993) *Drugs*, 45:931-952). The American Society of Anesthesiologists suggest 5HT₃ antagonists as the standard treatment and preventative therapy for PONV, used in 74-78% of patients. Each of the currently available 5-HT₃ antagonists suffers from one or more of the following deficiencies which limits its therapeutic utility: potency, duration of effect, window of therapeutic
15 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)
20 "5HT₃ 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-HT₃ antagonist, Zofran (Phillip Scuderi et al. (2002) "Single-Dose Oral Ondansetron
25 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-HT₃ 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-HT₃ receptor antagonists that have improved potency.

It is an object of the present invention to provide methods of inhibiting PONV using 5-HT₃ 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-HT₃ 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-HT₃ 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-HT₃ 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.).

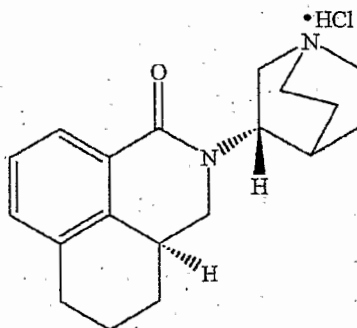
Throughout this specification the word “comprise,” or variations such as “comprises” or “comprising,” will be understood to imply the inclusion of a stated element, integer or step, or group of elements, integers or steps, but not the exclusion of any other element, integer or step, or group of elements, 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-1Hbenz[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
5 ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine and the like.

Methods of Administration

One embodiment of the present invention is premised upon the discovery that
10 palonosetron is surprisingly more potent than other 5-HT₃ 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
15 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
20 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
25 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.

5 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 $\mu\text{g/kg}$,
10 from about 0.3 to about 10 $\mu\text{g/kg}$, or from about 0.3 to about 1.0 $\mu\text{g/kg}$, are generally suitable, as are specific doses of about 0.3, 0.65 and 1.0 $\mu\text{g/kg}$. 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. Specific doses with which the
15 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 $\mu\text{g/kg}$, from about 1 to about 100
20 $\mu\text{g/kg}$, and from about 3 to about 10 $\mu\text{g/kg}$ 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
25 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.

10

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.

15

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.

20

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

25

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.

10 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 anesthetic 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
 15 HCl—(Nisentel), Anileridine, Benzitramide, Codeine, Dihydrocodeine, Diphenoxylate, Ethylmorphine, Etorphine Hydrochloride, Fentanyl, Granulated Opium, Hydrocodone, Hydromorphone (Dilaudid), Isomethadone, Levo-alphaacetylmethadol (LAMB), Levomethorphan, Levorphanol (Levo-Dromoran), Merperidine (Demeral, Pethadol), Metazocine, Methadone (Dolophine), Methadone
 20 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-phenylpiperidine, Pethidine-Intermediate-B ethyl-4-phenylpiperidine-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
5 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
10 [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 (Dorelin), Pentobarbital (Nembutal), Secobarbital (Seconal), 1-Any
15 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 ketone Methyl benzyl
20 ketone, immediate precursors to phencyclidine, 1-phenycyclohexylamine, 1-piperidineocyclohexanecarbonitrile 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 Expectorant Syrup with Codeine, Phenaphen with Codeine, Talwin; Pentazocine, all
25 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 -
5 105 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
10 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,
15 Other names for tiletamine are: 2-(ethylamino)-2-(2-thienyl)-cyclohexanone, Other names for Zolazepam are: 4-(2-fluorophenyl)-6,8-dihydro-1,3,8-trimethylpyrazolo-(3,4-e)(1,4)diazepin-7(1H)-one, flupyrazpon, Butabarbital—Butisol, Chloral Hydrate, Mephobarbital, Metharbital, Methyprylon, Phenobarbital, Sulfomethane, Sulfondiethylmethane, Sulfonethylmethane, and Talbutal.

20 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
25 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.

5 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
10 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
15 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
20 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.

25 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.

5 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,

10 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

15 physiological saline or phosphate buffered saline (PBS).

EXAMPLES

EXAMPLE 1. PREVENTION OF PONV USING A SINGLE INTRAVENOUS DOSE OF PALONOSETRON

5 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 N₂O plus an opiate. Study medication, palonosetron, was administered 10 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

15 * 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

20 *** 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), and 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- μ g/kg-, 1- μ g/kg-, 0.3- μ g/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% (32/62) of palonosetron 30- μ g/kg- and 1 μ g/kg-treated patients, respectively, and 59.6% (28/47) and 59.7% (40/67) of palonosetron 0.1- μ g/kg- and 0.3- μ g/kg-treated patients, respectively.

15

Table 3: Duration of Effect (hours) - IV						
	Placebo (n = 62)	0.1 μ g/kg (n = 47)	0.3 μ g/kg (n = 67)	1 μ g/kg (n = 62)	3 μ g/kg (n = 67)	30 μ g/kg (n = 67)
Emetic Episode (25 th Percentile)	2.3 16.3	2.2 > 24	8.4 > 24	21.8 > 24	4.9 > 24	> 24 > 24
Rescue (50 th percentile)	4.3	8.5	9.9	21.3	8.0	23.2
Time to Failure (50 th 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 $\mu\text{g/kg}$. 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 $\mu\text{g/kg}$) and a near-significant difference for 3.0- $\mu\text{g/kg}$ -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 $\mu\text{g/kg}$ 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 $\mu\text{g/kg}$.

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

- 5 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
- 10 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% (18/57) 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%) prochlorperazine (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-HT₃ 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 $\pm$ 0.5

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 $\pm$ 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
5 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
10 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:

- 15 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.
- 20 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
25 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 palonosetron is administered in an intravenous formulation having a pH of about 5.
- 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 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
15 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
20 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.
- 25 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
5 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
10 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
15 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
20 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
25 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.
- 5 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
10 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
5 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 administration 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
10 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
15 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.
- 20 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.
- 25 7. The use of one of the preceding claims wherein the composition is an
intravenous formulation comprising palonosetron 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
5 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
10 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.
- 15 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
20 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
25 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 thereof 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.

5 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.

10 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

International Application No.
PCT/EP2004/001558

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 A61K31/4748 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		
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) 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
☒ 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 7 May 2004		Date of mailing of the international search report 17/05/2004
Name and mailing address of the ISA 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		Authorized officer Bonzano, C

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/001558

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHELLY J ET AL: "Oral RS-25259 prevents postoperative nausea and vomiting following laparoscopic surgery" ANESTHESIOLOGY (HAGERSTOWN), vol. 85, no. 3A, 1996, page A21 XP008030467 Annual Meeting of the American Society of Anesthesiologists; New Orleans, Louisiana, USA; October 19-23, 1996 ISSN: 0003-3022 the whole document ---	1-29
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INTERNATIONAL SEARCH REPORT

Information on patent family members

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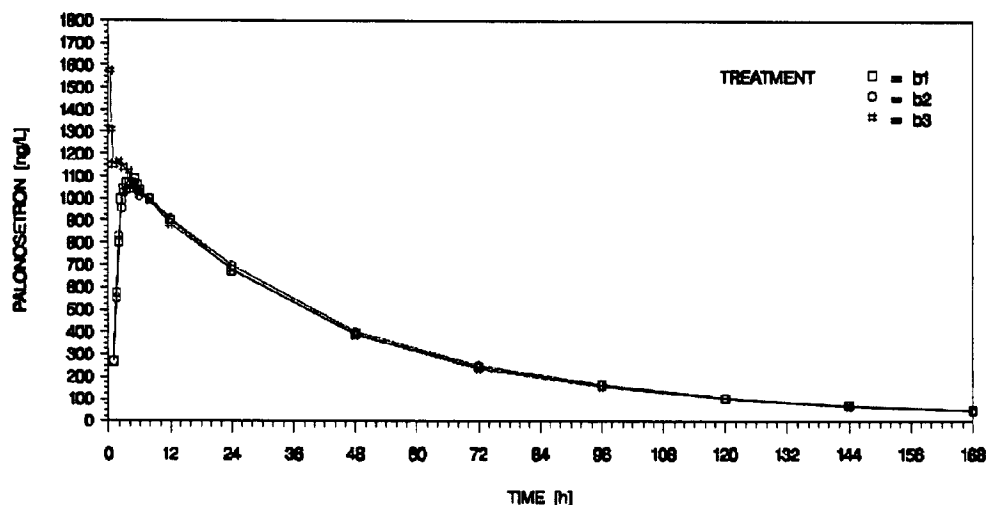
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(54) Title: SOFT CAPSULES COMPRISING PALONOSETRON HYDROCHLORIDE HAVING IMPROVED STABILITY AND BIOAVAILABILITY



(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.

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SOFT CAPSULES COMPRISING PALONOSETRON HYDROCHLORIDE HAVING IMPROVED STABILITY
AND BIOAVAILABILITYRELATIONSHIP 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

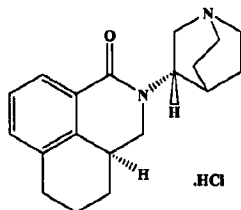
The present invention relates to palonosetron, and especially to solid oral dosage forms of palonosetron hydrochloride that meet demanding shelf stability requirements.

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-hydroxytryptamine 3 receptor precursor (5-HT₃ 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-HT₃ 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-HT₃ 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-1Hbenz[de] isoquinoline hydrochloride (CAS No. 119904-90-4); its empirical formula is C₁₉H₂₄N₂O•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/(cm²·24 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/(cm²·24 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/(cm²·24 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 $\leq 50 \text{ mg/m}^2$, cyclophosphamide $< 1500 \text{ mg/m}^2$, doxorubicin $> 25 \text{ mg/ms}$, epirubicin, irinotecan, or methotrexate $> 250 \text{ mg/m}^2$.

“Highly emetogenic chemotherapy” refers to chemotherapy in which the emetogenic potential is comparable or equivalent to the emetogenic potential of cisplatin $\geq 60 \text{ mg/m}^2$, cyclophosphamide $> 1500 \text{ mg/m}^2$, 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/(cm²·24 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/(cm²·24 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 cap 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.

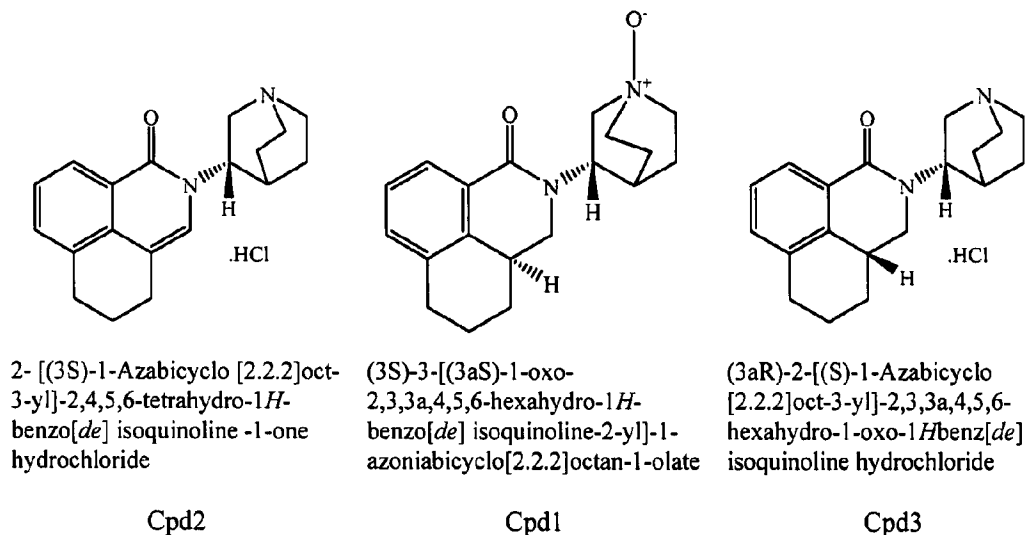
Yet another important feature of the dosage forms of the present invention, which also is preferred in any of the embodiments of the present invention, pertains to the dissolution of the dosage form, and in a preferred embodiment no less than about 75% of the palonosetron in the dosage form dissolves 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:

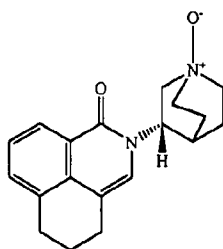


Compounds Cpd2 and Cpd3 are typically present, on an individual or combined basis relative to the palonosetron hydrochloride, in amounts of less than 1.0 wt.%, 0.75 wt.% or 0.5 wt.%, and/or greater than about 0.05 wt.%, 0.075 wt.% or 0.1 wt.%. Cpd2 and Cpd3 can be measured in the dosage form or in the 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.

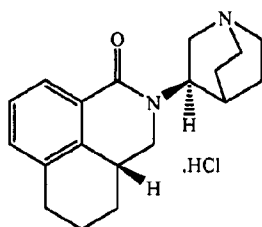
Therefore, in another embodiment the invention provides a solid oral dosage form comprising: (a) from about 0.05 to about 2.0 mg. of palonosetron or a pharmaceutically acceptable salt thereof; (b) one or more pharmaceutically acceptable excipients; (c) Cpd1 in an amount less than 3.0 wt.% based on the 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:



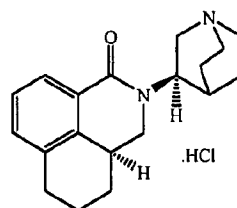
(3S)-3-(1-oxo-2,4,5,6-tetrahydro-1H-benzo[de]isoquinoline-2-yl)-1-azoniabicyclo[2.2.2]octan-1-olate

Cpd4



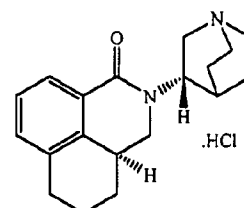
(3aR)-2-[(R)-1-Azabicyclo[2.2.2]oct-3yl]-2,3,3a,4,5,6-hexahydro-1-oxo-1H-benz[de]isoquinoline hydrochloride

Cpd5



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

Cpd6



(3aS)-2-[(S)-1-Azabicyclo[2.2.2]oct-3yl]-2,3,3a,4,5,6-hexahydro-1-oxo-1H-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/(cm²·24 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/(cm²·24 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 al., 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 al., "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 al., "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 al., "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 gastrointestinal 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
<i>Active drug substance</i> Palonosetron HCl	0.28 ^a	0.56 ^b	0.84 ^c
<i>Excipients</i> 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 $37.0 \pm 0.5^{\circ}\text{C}$. 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)			
Provisional Specification	90.0-110.0 %	% vs t ₀	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	97.7	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)			
	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)			
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	97.7	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 ₂ O/ 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 ₂ O/ 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 ₂ O/ 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		0.75 mg Palonosetron oral administration (formulation A)	0.75 mg Palonosetron oral administration (formulation B)	0.75 mg Palonosetron intravenous administration (3 x 0.25 mg i.v. Aloxi [®])
Palonosetron [unit]		N=33	N=33	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-∞) [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 linear scale (n=33).

Example 13 – Bioequivalence 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

Pharmacokinetic 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-∞} [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 linear 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/(cm²·24 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/(cm²·24 hr. atm).
 - 10) The capsule of claim 1 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 an oxygen permeability of less than about 1.0×10^{-3} ml·cm/(cm²·24 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 Cpd 1 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/(cm²·24 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/(cm²·24 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.

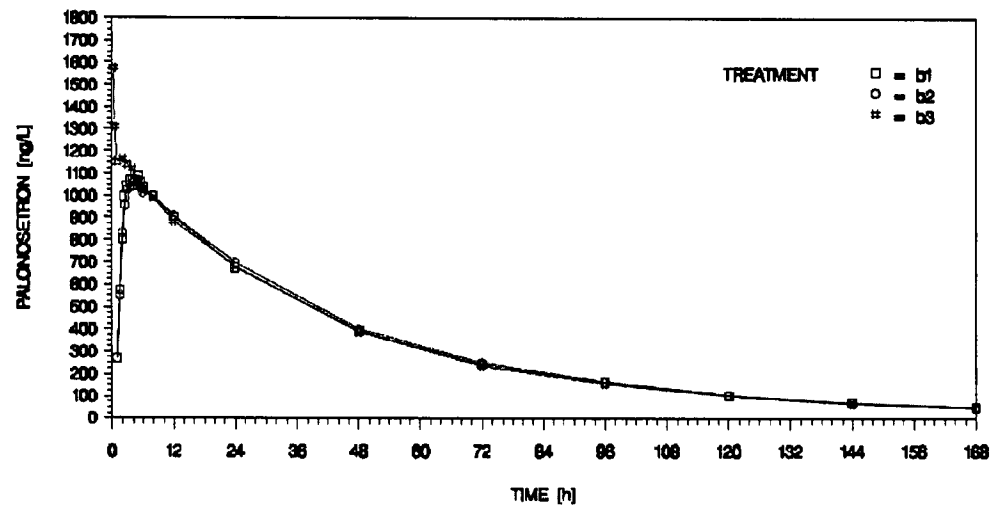


FIGURE 1

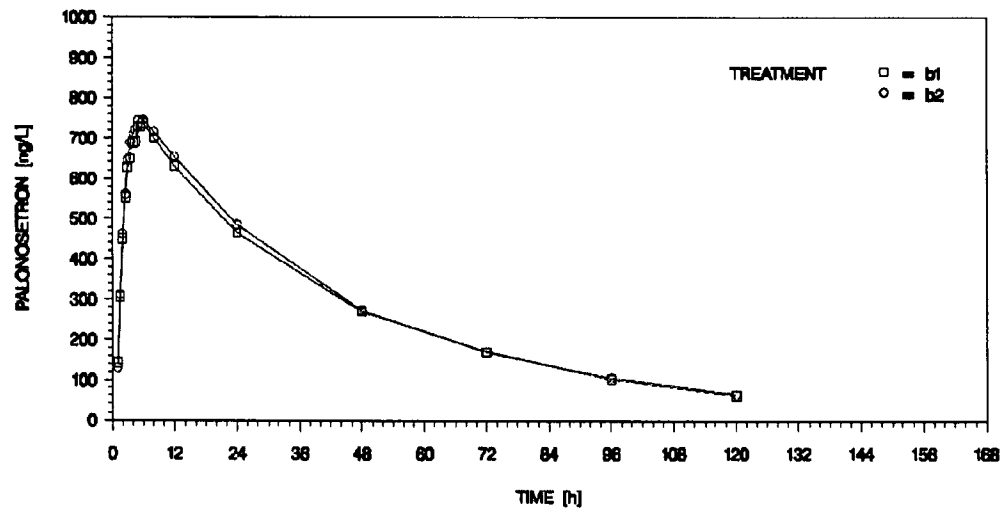


FIGURE 2

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
- *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)
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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

17 January 2008

Date of mailing of the international search report

28/01/2008

Name and mailing address of the ISA/

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Authorized officer

GIMENEZ MIRALLES, J

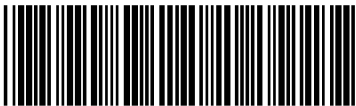
INTERNATIONAL SEARCH REPORT

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
WO 2004045615 A	03-06-2004	AU 2003302072 A1 CA 2505990 A1 DE 10393729 T5 JP 2006508977 T	15-06-2004 03-06-2004 13-10-2005 16-03-2006
WO 2005065652 A	21-07-2005	CA 2547712 A1 EP 1706100 A1 JP 2007517859 T US 2007190080 A1	21-07-2005 04-10-2006 05-07-2007 16-08-2007
WO 02053131 A	11-07-2002	CA 2432362 A1 EP 1345590 A1 FR 2818905 A1 US 2004052824 A1	11-07-2002 24-09-2003 05-07-2002 18-03-2004

Search Notes 	Application/Control No. 15/003,327	Applicant(s)/Patent Under Reexamination TRENTO et al.
	Examiner WALTER E WEBB	Art Unit 1612

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

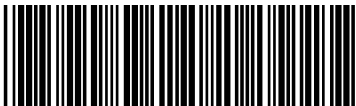
US Classification - Searched*			
Class	Subclass	Date	Examiner
514	17.7	2/26/2016	WW

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

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

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
A61K	31/434	9/1/2017	WW

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Issue Classification 	Application/Control No. 15/003,327	Applicant(s)/Patent Under Reexamination TRENTO et al.
	Examiner WALTER E WEBB	Art Unit 1612

CPC						
Symbol					Type	Version
A61K	/	31	/	496	F	2013-01-01
A61K	/	9	/	4808	I	2013-01-01
A61K	/	31	/	4178	I	2013-01-01
A61K	/	31	/	473	I	2013-01-01
A61K	/	31	/	573	I	2013-01-01
A61K	/	45	/	06	I	2013-01-01
A61K	/	9	/	2054	I	2013-01-01
A61K	/	9	/	4858	I	2013-01-01
A61K	/	9	/	0053	I	2013-01-01
Y10S	/	514	/	872	A	2013-01-01

CPC Combination Sets								
Symbol					Type	Set	Ranking	Version
A61K	/	31	/	4178	I	1	1	2013-01-01
A61K	/	2300	/	00	A	1	2	2013-01-01
A61K	/	31	/	473	I	2	1	2013-01-01
A61K	/	2300	/	00	A	2	2	2013-01-01
A61K	/	31	/	496	I	3	1	2013-01-01
A61K	/	2300	/	00	A	3	2	2013-01-01
A61K	/	31	/	573	I	4	1	2013-01-01
A61K	/	2300	/	00	A	4	2	2013-01-01

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	23	
/WALTER E WEBB/ Primary Examiner, Art Unit 1612	01 December 2017	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	Claim 1	None

Issue Classification 	Application/Control No. 15/003,327	Applicant(s)/Patent Under Reexamination TRENTO et al.
	Examiner WALTER E WEBB	Art Unit 1612

INTERNATIONAL CLASSIFICATION				
CLAIMED				
A61K	/	496	/	
A61K	/	06	/	
A61K	/	573	/	
NON-CLAIMED				
	/		/	

US ORIGINAL CLASSIFICATION	
CLASS	SUBCLASS
514	17.7

CROSS REFERENCES(S)						
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)					
514	183	185	187	188	872	

NONE (Assistant Examiner) _____ (Date) _____		Total Claims Allowed: 23	
/WALTER E WEBB/ Primary Examiner, Art Unit 1612 (Primary Examiner) _____ (Date) _____		01 December 2017 O.G. Print Claim(s) Claim 1	O.G. Print Figure None

Issue Classification 	Application/Control No. 15/003,327	Applicant(s)/Patent Under Reexamination TRENTO et al.
	Examiner WALTER E WEBB	Art Unit 1612

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☒ T.D. ☐ R.1.47

CLAIMS															
Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	16	10	53	19	67										
2	17	11	54	20	68										
3	18	12	55	21	69										
4	21	13	56	22	70										
5	23	14	58	23	71										
6	24	15	59												
7	25	16	60												
8	26	17	61												
9	52	18	64												

NONE (Assistant Examiner) _____ (Date) _____		Total Claims Allowed: 23	
/WALTER E WEBB/ Primary Examiner, Art Unit 1612 (Primary Examiner) _____ (Date) 01 December 2017		O.G. Print Claim(s) Claim 1	O.G. Print Figure None



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NOTICE OF ALLOWANCE AND FEE(S) DUE

140619 7590 12/11/2017
Sullivan IP Solutions, LLC
PO Box 2252
New York, NY 10163

EXAMINER

WEBB, WALTER E

ART UNIT

PAPER NUMBER

1612

DATE MAILED: 12/11/2017

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/003,327	01/21/2016	Fabio TRENTO	HHC002US6/CO001	1097

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	UNDISCOUNTED	\$960	\$0	\$0	\$960	03/12/2018

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.

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**Complete and send this form, together with applicable fee(s), to: Mail Mail Stop ISSUE FEE
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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)

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.

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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.
15/003,327	01/21/2016	Fabio TRENTO	HHC002US6/CO001	1097

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	UNDISCOUNTED	\$960	\$0	\$0	\$960	03/12/2018

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**

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. ~~Assignment is required~~ 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 _____

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☐ Payment by credit card. Form PTO-2038 is attached.

☐ The director is hereby authorized to charge the required fee(s), any deficiency, or credits 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

☐ Applicant asserting small entity status. See 37 CFR 1.27

☐ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
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Authorized Signature _____ Date _____

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/003,327	01/21/2016	Fabio TRENTA	HHC002US6/CO001	1097
140619	7590	12/11/2017	EXAMINER	
Sullivan IP Solutions, LLC PO Box 2252 New York, NY 10163			WEBB, WALTER E	
			ART UNIT	PAPER NUMBER
			1612	
DATE MAILED: 12/11/2017				

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b) (Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance. Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 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.

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.
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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 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. 15/003,327	Applicant(s) TRENTO et al.	
	Examiner WALTER E WEBB	Art Unit 1612	AIA 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 Applicant's communication filed 11/21/2017 .
☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____ .

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

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

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

Certified copies:

a) ☐ All b) ☐ Some *c) ☐ None of the:

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

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

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

* Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file areply 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 11/21/2017 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 E WEBB/
Primary Examiner, Art Unit 1612

Continuation of 3. The allowed claim(s) is/are: 16-18,21,23-26,52-56,58-61,64 and 67-71

Doc code: IDS

PTO/SB/08a (01-10)

Doc description: Information Disclosure Statement (IDS) Filed

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	15003327
	Filing Date	2016-01-21
	First Named Inventor	Fabio TRENTO
	Art Unit	1612
	Examiner Name	Walter E. Webb
	Attorney Docket Number	HHC002US6/CO001

U.S.PATENTS						Remove
Examiner Initial*	Cite No	Patent Number	Kind Code ¹	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	6297375		2001-10-02	Bos , et al.	
	2	6747026		2004-06-08	Hoffmann, et al.	
	3	6806370		2004-10-19	Hoffmann, et al.	

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	1	2008/049552	WO	A1	2008-05-02	HELSINN HEALTHCARE S.A., et al.		

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	15003327
Filing Date	2016-01-21
First Named Inventor	Fabio TRENTO
Art Unit	1612
Examiner Name	Walter E. Webb
Attorney Docket Number	HHC002US6/CO001

2	2004/073714	WO	A1	2004-09-02	HELSINN HEALTHCARE S.A., et al.
3	2004/067005	WO	A1	2004-08-12	HELSINN HEALTHCARE S.A., et al.

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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	Grunberg et al., SUPPORT CANCER CARE (2009) 17:589-594	
	2	Jordan et al., THE ONCOLOGIST, Vol. 12, No. 9, 1143-1150, September 2007	
	3	Goldhill Advances in Drug Discovery 2006	
	4	Herrstedt J Antiemetics: an update and the MASCC guidelines applied in clinical practice; Nature Clin Practice Jan 2008, 5:32-43.	
	5	Muchatuta Ther & Risk Clin Management 2009, 5:21 -34	
	6	Aapro M Ther & Risk Clin Management 2007, 3:1009-1020	
	7	Yang, et al. Adis Drug Evaluation Drugs 2009, 69: 2257-2278	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)

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Examiner Name	Walter E. Webb
Attorney Docket Number	HHC002US6/CO001

8	PER in respect of PCT/IB2010/003106 (W02011061622); May 22, 2012.
9	Karin, et al.; The Oncologist 2007, 12:1143-1150.
10	EMA "Guideline On Pharmaceutical Fixed Combination Products" 18 Dec 2006.
11	Rizzi, Anna et al., "In vitro and in vivo pharmacological characterization of the novel NK1 receptor selective antagonist Netupitant" 23.06.2012, [cited 23.06.2012] Peptides 37 (2012) 86-97.
12	Non-exhaustive list of fourteen NK-1 antagonist; D18. 11/21/2017
13	Clinical study report; NETU-08-18; INVESTIGATIONAL PLAN; June 12, 2013.
14	Clinical study report; Single-dose, multi-center, randomized, double-blind, double-dummy, parallel group study to assess the efficacy and safety of ... PALO-10-01; June 5, 2013.
15	Decision rejecting the opposition (Art. 101(2) EPC) issued in corresponding EP application no. 14151676.5 on September 26, 2017.

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Examiner Signature	/WALTER E WEBB/	Date Considered	12/01/2017
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*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.

<i>Index of Claims</i> 	Application/Control No. 15/003,327	Applicant(s)/Patent Under Reexamination TRENTO et al.
	Examiner WALTER E WEBB	Art Unit 1612

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

CLAIMS										
☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☒ T.D. ☐ R.1.47										
CLAIM		DATE								
Final	Original	03/10/2016	09/01/2016	03/13/2017	09/01/2017	12/01/2017				
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	41	-	-	-	-	-				
	42	-	-	-	-	-				

<i>Index of Claims</i> 	Application/Control No. 15/003,327	Applicant(s)/Patent Under Reexamination TRENTO et al.
	Examiner WALTER E WEBB	Art Unit 1612

CLAIM		DATE									
Final	Original	03/10/2016	09/01/2016	03/13/2017	09/01/2017	12/01/2017					
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	51	-	-	-	-	-					
9	52	✓	✓	✓	=	=					
10	53	✓	✓	✓	=	=					
11	54	✓	✓	✓	=	=					
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13	56	✓	✓	✓	=	=					
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	65			N	-	-					
	66			N	-	-					
19	67			N	=	=					
20	68			N	=	=					
21	69			N	=	=					
22	70			N	=	=					
23	71			N	=	=					

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number	15003327
	Filing Date	2016-01-21
	First Named Inventor	Fabio TRENTA
	Art Unit	1612
	Examiner Name	WEBB, WALTER E
	Attorney Docket Number	HHC002US6/CO001

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		15003327
	Filing Date		2016-01-21
	First Named Inventor	Fabio TRENTO	
	Art Unit	1612	
	Examiner Name	WEBB, WALTER E	
	Attorney Docket Number	HHC002US6/CO001	

1	Rubenstein, et al. New Approaches to Chemotherapy Induced Nausea and Vomiting: From Neuropharmacology to Clinical Investigations; Cancer J 2006;12:341-34.
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Examiner Signature		Date Considered	
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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.

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Application Number	15003327
Filing Date	2016-01-21
First Named Inventor	Fabio TRENT0
Art Unit	1612
Examiner Name	WEBB, WALTER E
Attorney Docket Number	HHC002US6/CO001

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)	2018-01-03
Name/Print	Clark G. Sullivan	Registration Number	36942

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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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 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.
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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.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:	)	
TRENTO et al.	)	Customer No.: 140619
	)	
Application No.: 15/003,327	)	Confirmation No.: 1097
	)	
Filing Date: 01-21-2016	)	Art Unit: 1612
	)	
For: COMPOSITIONS AND METHODS FOR	)	Examiner: Walter E. Webb
TREATING CENTRALLY MEDIATED	)	
NAUSEA AND VOMITING	)	

INFORMATION DISCLOSURE STATEMENT

Commissioner for Patents
Alexandria, VA 22313-1450

Dear Sir:

Filed currently herewith is a form SB08 in compliance with 37 C.F.R. §§ 1.56, 1.97 and 1.98.

37 CFR 1.97(e) Statement

The undersigned hereby certifies:

(1) 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 § 1.56(c) more than three months prior to the filing of the information disclosure statement.

This submission does not represent that a search has been made or that no better art exists and does not constitute an admission that each or all of the listed documents are material or constitute “prior art.” If the Examiner applies any of the documents as prior art against any claim in the application and Applicant determines that the cited documents do not constitute “prior art”

under United States law, Applicant reserves the right to present to the U.S. Patent and Trademark Office the relevant facts and law regarding the appropriate status of such documents.

If there is any fee due in connection with the filing of this statement, please charge the fee to Deposit Account No. 600254.

Dated: January 3, 2018

Respectfully submitted,

By: /Clark G. Sullivan/
Clark G. Sullivan
Reg. No. 36,942
Customer No. 140619

Electronic Acknowledgement Receipt

EFS ID:	31387217
Application Number:	15003327
International Application Number:	
Confirmation Number:	1097
Title of Invention:	COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING
First Named Inventor/Applicant Name:	Fabio TRENTO
Customer Number:	140619
Filer:	Clark G. Sullivan
Filer Authorized By:	
Attorney Docket Number:	HHC002US6/CO001
Receipt Date:	03-JAN-2018
Filing Date:	21-JAN-2016
Time Stamp:	09:02:08
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no
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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Non Patent Literature	Rubenstein_2006.pdf	1403611	no	7
			8855a0809f1fb07344ca34ad55e2c4e9ed01f351		

Warnings:

Information:					
2	Information Disclosure Statement (IDS) Form (SB08)	US6_Jan2018_IDS_SB08.pdf	612056 ab08dd8f45050d840a2a6c929452353d69c25412	no	4
Warnings:					
Information:					
A U.S. Patent Number Citation or a U.S. Publication Number Citation is required in the Information Disclosure Statement (IDS) form for autoloading of data into USPTO systems. You may remove the form to add the required data in order to correct the Informational Message if you are citing U.S. References. If you chose not to include U.S. References, the image of the form will be processed and be made available within the Image File Wrapper (IFW) system. However, no data will be extracted from this form. Any additional data such as Foreign Patent Documents or Non Patent Literature will be manually reviewed and keyed into USPTO systems.					
3	Transmittal Letter	US6_Jan2018_IDS_Transmittal.pdf	52735 dc3fa1ff1036f3cbbde77b8e5ec3944a1ef0fdde	no	2
Warnings:					
Information:					
Total Files Size (in bytes):			2068402		
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Document code: WFEE

United States Patent and Trademark Office
Sales Receipt for Accounting Date: 01/10/2018

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		01	FC : 1806	180.00	DA	

Doc code: IDS

PTO/SB/08a (01-10)

Doc description: Information Disclosure Statement (IDS) Filed

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	15003327
	Filing Date	2016-01-21
	First Named Inventor	Fabio TRENTO
	Art Unit	1612
	Examiner Name	WEBB, WALTER E
	Attorney Docket Number	HHC002US6/CO001

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**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	15003327
Filing Date	2016-01-21
First Named Inventor	Fabio TRENTO
Art Unit	1612
Examiner Name	WEBB, WALTER E
Attorney Docket Number	HHC002US6/CO001

1	Rubenstein, et al. New Approaches to Chemotherapy Induced Nausea and Vomiting: From Neuropharmacology to Clinical Investigations; Cancer J 2006;12:341-34.
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Examiner Signature	/WALTER E WEBB/	Date Considered	01/24/2018
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*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.



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/003,327	01/21/2016	Fabio TRENTO	HHC002US6/CO001	1097
140619	7590	01/29/2018		
Sullivan IP Solutions, LLC			EXAMINER	
PO Box 2252			WEBB, WALTER E	
New York, NEW YORK 10163				
			ART UNIT	PAPER NUMBER
			1612	
			NOTIFICATION DATE	DELIVERY MODE
			01/29/2018	ELECTRONIC

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

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

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

clark@sullivanipsolutions.com

docketing@sullivanipsolutions.com

**UNITED STATES DEPARTMENT OF COMMERCE****U.S. Patent and Trademark Office**

Address: COMMISSIONER FOR PATENTS

P.O. Box 1450

Alexandria, Virginia 22313-1450

APPLICATION NO./ CONTROL NO.	FILING DATE	FIRST NAMED INVENTOR/ PATENT IN REEXAMINATION	ATTORNEY DOCKET NO.
15/003,327	01/21/2016	TRENTO et al.	HHC002US6/CO001

Sullivan IP Solutions, LLC PO Box 2252 New York, 10163		EXAMINER	
		WALTER E WEBB	
		ART UNIT	PAPER
		1612	20180124

DATE MAILED: _____

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

Commissioner for Patents

The IDS filed 1/3/2018 has been considered.

/WALTER E WEBB/
Primary Examiner, Art Unit 1612

Document Description: Issue Fee Payment (PTO-85B)

Issue Fee Transmittal Form

Application Number	Filing Date	First Named Inventor	Atty. Docket No.	Confirmation No.
15003327	21-Jan-2016	Fabio TRENTO	HHC002US6/CO001	1097

TITLE OF INVENTION :

COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING

Entity Status	Application Type	Art Unit	Class - Subclass	EXAMINER
Regular Undiscounted	Utility under 35 USC 111(a)	1612	017700	WALTER WEBB
Issue Fee Due	Publication Due	Total Fee(s) Due	Date Due	Prev. Paid Fee
\$960	\$0	\$960	12-Mar-2018	\$0

1.Change of Correspondence Address and/or Indication Of Fee Address (37 CFR 1.33 & 1.363)

Current Correspondence Address:	Current Indicated Fee Address :
140619 Sullivan IP Solutions, LLC PO Box 2252 New York NY 10163 UNITED STATES 404-483-9360 ~~clark@sullivanipsolutions.com~~	
☐ Change of correspondence address requested, system generated AIA/122-EFS form attached	☐ Fee Address indication requested, system generated SB/47-EFS form attached

2.Entity Status**Change in Entity Status**

Applicant certifying micro entity status; system generated Micro Entity certification form attached. See 37 CFR 1.29.

Note: Absent a valid certification of micro entity status, issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment. If this box is checked, you will be prompted to choose a micro entity status on the gross income basis (37 CFR 1.29(a)) or the institution of higher education basis (37 CFR 1.29(d)), and make the applicable certification online.



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.



Document Description: Issue Fee Payment (PTO-85B)

3.The Following Fee(s) Are Submitted:

☒ Issue Fee

☐ I authorize USPTO to apply my previously paid issue fee to the current fees due

☐ Publication Fee

☐ The Director is hereby authorized to apply my previously paid issue fee to the current fee due and to charge deficient fees to Deposit Account Number _____

☐ Advance Order - # of copies _____

☒ If in **addition** to the payment of the issue fee amount submitted with this form, there are any discrepancies in any amount(s) due, the Director is authorized to charge any deficiency, or credit any overpayment, to Deposit Account Number 140619.
The **issue fee must be submitted** with this form. **If payment of the issue fee does not accompany this form, checking this box and providing a deposit account number will NOT be effective to satisfy full payment of the fee(s) due.**

4.Firm and/or Attorney Names To Be Printed

NOTE: If no name is listed, no name will be printed
For printing on the patent front page, list to be displayed as entered

1. Clark G. Sullivan
2.
3.

5.Assignee Name(s) and Residence Data To Be Printed

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.

Name	City	State	Country	Category
Helsinn Healthcare SA	Lugano/ Pazzallo		switzerland	corporation

6.Signature

I certify, in accordance with 37 CFR 1.4(d)(4) that I am an attorney or agent registered to practice before the Patent and Trademark Office who has filed and has been granted power of attorney in this application. I also certify that this Fee(s) Transmittal form is being transmitted to the USPTO via EFS-WEB on the date indicated below.

Signature	/Clark Sullivan/	Date	03-08-2018
Name	Clark G. Sullivan	Registration Number	36942

Electronic Patent Application Fee Transmittal

Application Number:	15003327			
Filing Date:	21-Jan-2016			
Title of Invention:	COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING			
First Named Inventor/Applicant Name:	Fabio TRENTO			
Filer:	Clark G. Sullivan			
Attorney Docket Number:	HHC002US6/CO001			
Filed as Large Entity				
Filing Fees for Utility under 35 USC 111(a)				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
UTILITY APPL ISSUE FEE	1501	1	960	960
PUBL. FEE- EARLY, VOLUNTARY, OR NORMAL	1504	1	0	0
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
Total in USD (\$)				960

Electronic Acknowledgement Receipt

EFS ID:	31992361
Application Number:	15003327
International Application Number:	
Confirmation Number:	1097
Title of Invention:	COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING
First Named Inventor/Applicant Name:	Fabio TRENTO
Customer Number:	140619
Filer:	Clark G. Sullivan
Filer Authorized By:	
Attorney Docket Number:	HHC002US6/CO001
Receipt Date:	08-MAR-2018
Filing Date:	21-JAN-2016
Time Stamp:	10:43:00
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	\$960
RAM confirmation Number	030818INTEFSW10425800
Deposit Account	600254
Authorized User	Clark Sullivan

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

37 CFR 1.20 (Post Issuance fees)

37 CFR 1.21 (Miscellaneous fees and charges)

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)	Web85b.pdf	45966	no	2
			eb924734c7eb061ed25a68913294b96b9285a4d0		
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	32132	no	2
			a98a6c5e8deb27939601e1c8ee721d748aed785a		
Warnings:					
Information:					
Total Files Size (in bytes):			78098		
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.					

Receipt date: 06/10/2016

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	15003327
Filing Date	2016-01-21
First Named Inventor	Fabio TRENTO
Art Unit	1612
Examiner Name	Walter Webb
Attorney Docket Number	HHC002US6

Change(s) applied

to document, /L.H./ 2 9/25/2017	20070009676	01/2007 ~~2007-08-30~~	Pfizer Tamagawa et al.
3			

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	Kind Code ⁴	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear	T ⁵
	1	2008049552	WO		2008-05-02	Helsinn Healthcare		
	2	2004067005	WO		2004-08-12	Helsinn Healthcare		
	3	2004073714	WO		2004-09-02	Helsinn Healthcare		

If you wish to add additional Foreign Patent Document citation information please click the Add button. **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	Japanese Office Action dated November 19, 2014, which issued during prosecution of Japanese Patent Application No. 2012-539433.	
	2	Torsten HOFFMANN, et al., "Design and synthesis of a novel, achiral class of highly potent and selective, orally active neurokinin-1 receptor antagonists", Bioorganic & Medicinal Chemistry Letters 16 (2006) 1362-1365.	



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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/003,327	04/17/2018	9943515	HHC002US6/CO001	1097

140619 7590 03/28/2018
Sullivan IP Solutions, LLC
PO Box 2252
New York, NY 10163

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, ITALY;
Helsinn Healthcare SA, Lugano/Pazzallo, SWITZERLAND;
Sergio CANTOREGGI, Cagiallo, SWITZERLAND;
Giorgia ROSSI, Cernobbio, ITALY;
Roberta CANNELLA, Varese, ITALY;
Daniele BONADEO, Casalzuigno, ITALY;

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