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UTILITY PATENT APPLICATION TRANSMITTAL

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

Attorney Docket No.	244168.000015US4
First Named Inventor	Fabio TRENTO
Title	COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSE
Express Mail Label No.	

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

1. ☐ **Fee Transmittal Form** (PTO/SB/17 or equivalent)
2. ☐ **Applicant asserts small entity status.** See 37 CFR 1.27
3. ☐ **Applicant certifies micro entity status.** See 37 CFR 1.29. Applicant must attach form PTO/SB/15A or B or equivalent.
4. ☑ **Specification** [*Total Pages* 36] Both the claims and abstract must start on a new page. *(See MPEP § 608.01(a) for information on the preferred arrangement)*
5. ☑ **Drawing(s)** (35 U.S.C. 113) [*Total Sheets* 5]
6. **Inventor's Oath or Declaration** [*Total Pages* ____] *(including substitute statements under 37 CFR 1.64 and assignments serving as an oath or declaration under 37 CFR 1.63(e))*
   a. ☐ Newly executed (original or copy)
   b. ☐ A copy from a prior application (37 CFR 1.63(d))
7. ☑ **Application Data Sheet** ** See note below.* See 37 CFR 1.76 (PTO/AIA/14 or equivalent)
8. **CD-ROM or CD-R** in duplicate, large table, or Computer Program (*Appendix*)
   ☐ Landscape Table on CD
9. **Nucleotide and/or Amino Acid Sequence Submission** (*if applicable, items a. – c. are required*)
   a. ☐ Computer Readable Form (CRF)
   b. ☐ Specification Sequence Listing on:
      i. ☐ CD-ROM or CD-R (2 copies); or
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ACCOMPANYING APPLICATION PAPERS

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

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

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Signature	/Heather Morehouse Ettinger/	Date	November 1, 2013
Name (Print/Type)	Heather Morehouse Ettinger	Registration No. (Attorney/Agent)	51658

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NONPROVISIONAL APPLICATION FOR UNITED STATES PATENT

for

COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING

by:

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

COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING

CROSS-REFERENCE TO RELATED APPLICATIONS

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

FIELD OF THE INVENTION

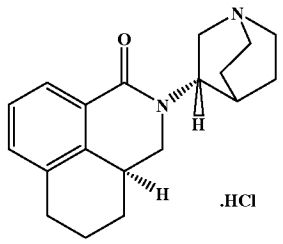
The present invention relates to the use of centrally acting NK_1 antagonists to treat nausea and vomiting, particular nausea and vomiting induced by highly emetogenic chemotherapy, and to the treatment of such nausea and vomiting over multiple consecutive days. The present invention also relates to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

BACKGROUND OF THE INVENTION

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

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

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

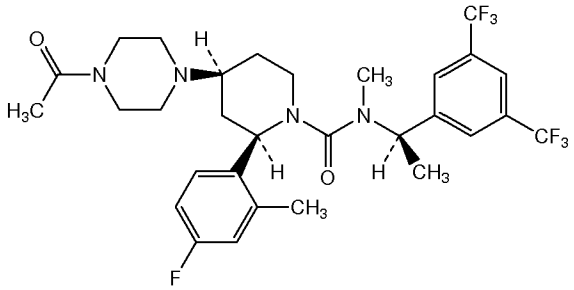


Methods of synthesizing palonosetron are described in U.S. Patent Nos. 5,202,333 and 5,510,486. Pharmaceutically acceptably dosage forms are described in PCT publications WO 2004/067005 and WO 2008/049552 from Helsinn Healthcare.

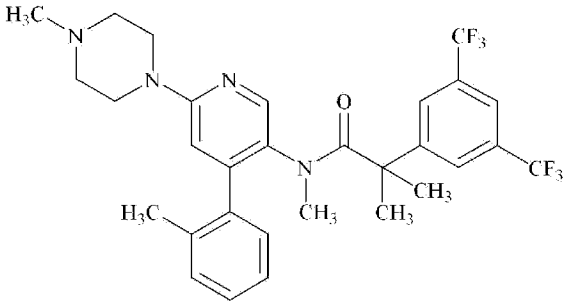
NK_1 antagonists have also recently emerged as a tool for combating nausea and vomiting from emetogenic medical procedures. Most recently, aprepitant was approved by the Food and Drug Administration ("FDA") for use in combination with other anti-emetic agents for the prevention of nausea and vomiting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

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

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



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



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

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

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

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

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

OBJECTS OF THE INVENTION

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

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

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

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

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

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

SUMMARY OF THE INVENTION

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

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

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

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

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

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

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

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

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

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

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

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

BRIEF DESCRIPTION OF THE DRAWINGS

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

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

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

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

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

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

DETAILED DESCRIPTION OF THE INVENTION

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

Definitions and Use of Terms

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Methods of Treatment

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

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

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

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

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

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

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

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

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

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

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

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

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

Pharmaceutical Compositions

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

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

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

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

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

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

Combined Oral Dosage Forms

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

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

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

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

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

Hard Outer Shell

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

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

Soft-Gel Capsule

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

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

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

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

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

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

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

Tablet

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

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

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

Application of The Combined Oral Dosage Forms

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

EXAMPLES

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

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

EXAMPLE 1 – PREPARATION OF ORAL DOSAGE FORM

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

TABLE 1: REPRESENTATIVE SOFT-GEL FORMULATION

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

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

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

TABLE 2: REPRESENTATIVE TABLET FORMULATION

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

EXAMPLE 2 – PHARMACOKINETICS OF COMBINED DOSAGE FORM

Objective

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

Methods

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

The following treatments were investigated:

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

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

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

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

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

Results

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

Table 3: Summary of Netupitant Pharmacokinetic Parameters

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

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

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

Table 4: Summary of Palonosetron Pharmacokinetic Parameters

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

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

EXAMPLE 3: NETUPITANT + DEXAMETHASONE DRUG INTERACTION STUDY

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

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

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

EXAMPLE 4: NETUPITANT PET RECEPTOR OCCUPANCY STUDY

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

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

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

EXAMPLE 5: CLINICAL EFFICACY STUDY

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

EXAMPLE 7: COMPARATIVE RESULTS OF APREPITANT DOSING REGIMEN

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

TABLE 7

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

TABLE 8

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

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

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

****

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

CLAIMS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

a) an outer shell;

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

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

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

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

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

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

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

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

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

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

42) An orally administered capsule dosage form comprising:

a) an outer shell;

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

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

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

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

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

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

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

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

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

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

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

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

COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING

ABSTRACT

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

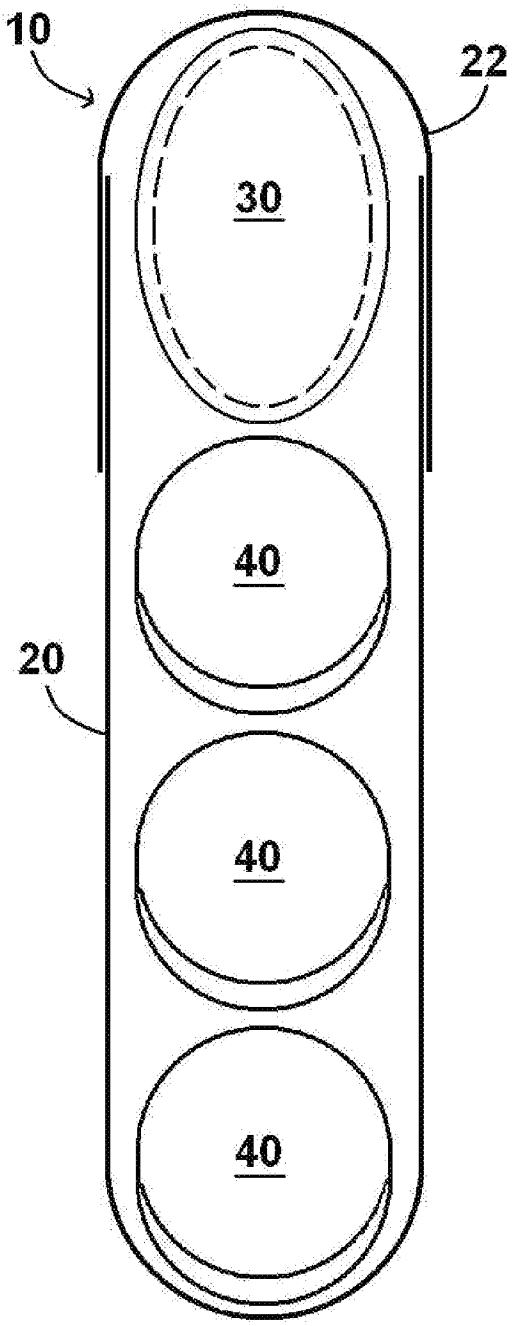


Figure 1

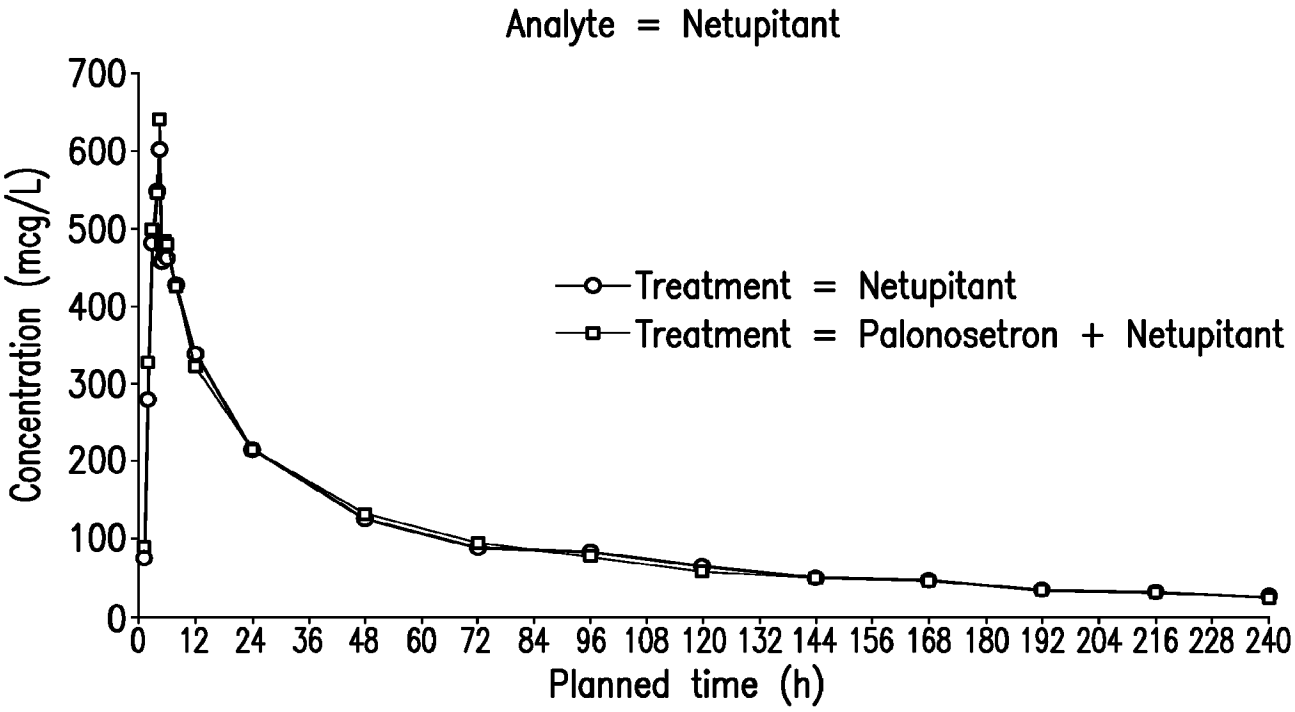

Analyte = Netupitant
Concentration (mcg/L)
700
600
500
400
300
200
100
0
0 12 24 36 48 60 72 84 96 108 120 132 144 156 168 180 192 204 216 228 240
Planned time (h)
Treatment = Netupitant
Treatment = Palonosetron + Netupitant

FIG.2

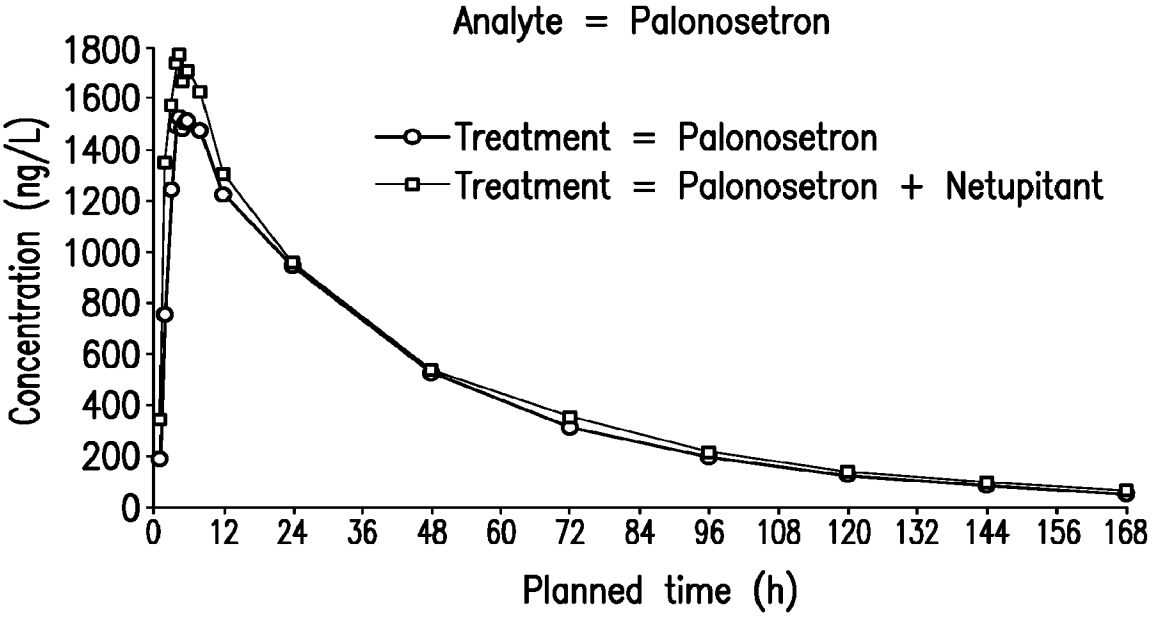

Analyte = Palonosetron
Treatment = Palonosetron
Treatment = Palonosetron + Netupitant
Concentration (ng/L)
1800
1600
1400
1200
1000
800
600
400
200
0
0
12
24
36
48
60
72
84
96
108
120
132
144
156
168
Planned time (h)

FIG.3

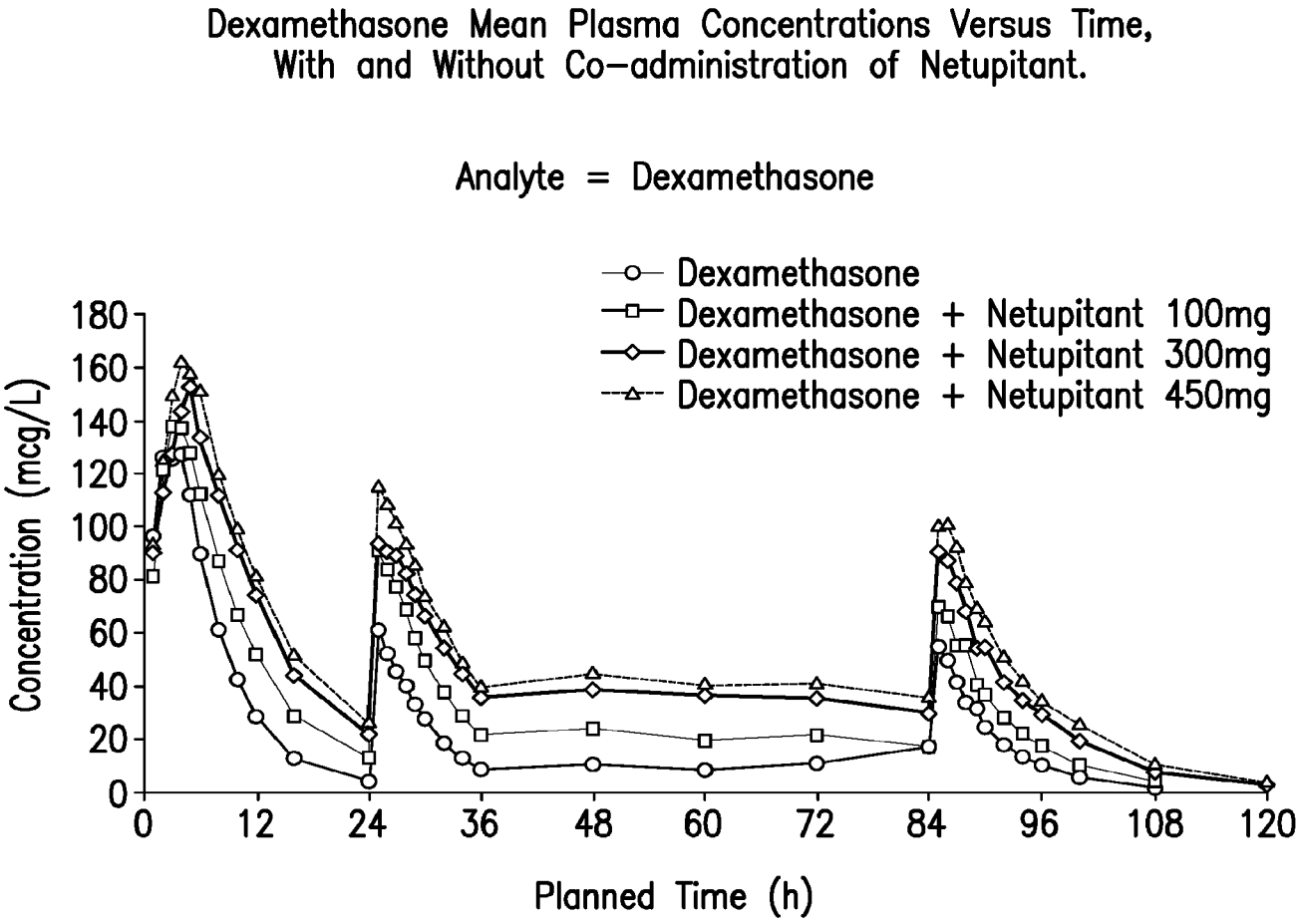
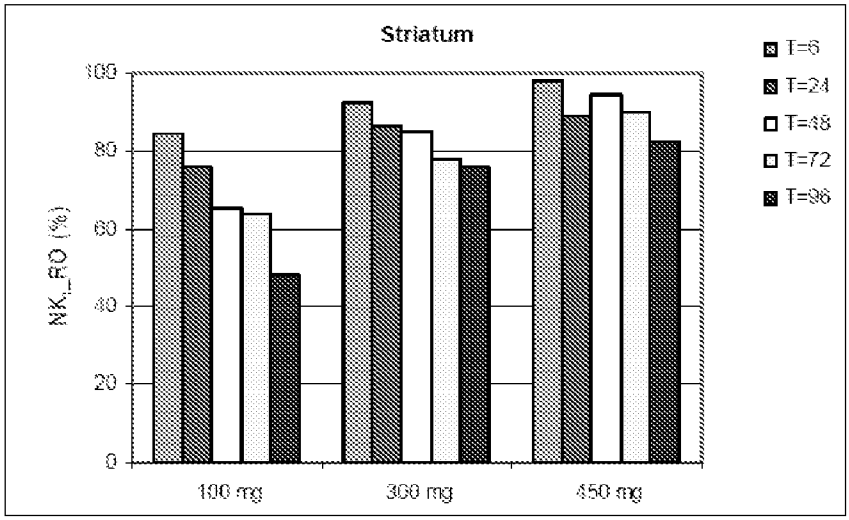

Dexamethasone Mean Plasma Concentrations Versus Time,
With and Without Co-administration of Netupitant.
Analyte = Dexamethasone
Dexamethasone
Dexamethasone + Netupitant 100mg
Dexamethasone + Netupitant 300mg
Dexamethasone + Netupitant 450mg
Concentration (mcg/L)
180
160
140
120
100
80
60
40
20
0
0
12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

FIG.4


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

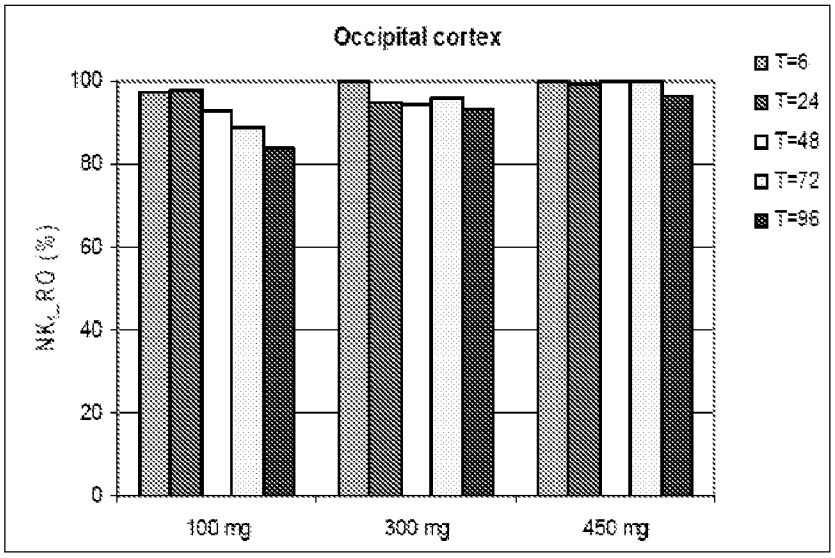

Occipital cortex
NK_RO (%)
100
80
60
40
20
0
100 mg
300 mg
450 mg
T=6
T=24
T=48
T=72
T=96

FIG. 5

Docket No.: 244168.000015US4
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Fabio Trento et al.	Customer No.: 06980
Application No.: Submitted herewith (Continuation of U.S. Application No. 13/077,462)	Confirmation No.: Not yet assigned
Filing Date: Submitted herewith	Art Unit: Not yet assigned
For: COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING	Examiner: Not yet assigned

PRELIMINARY AMENDMENT

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

Dear Sir:

INTRODUCTORY COMMENTS

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

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

Remarks begin on page 3 of this paper.

AMENDMENTS TO THE SPECIFICATION

On Page 1 of the Specification, please replace the paragraph after the heading "CROSS-REFERENCE TO RELATED APPLICATIONS", with the following paragraph:

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

REMARKS

The specification has been amended to make reference to and incorporate by reference its priority documents. No new matter is added by this amendment.

Dated: November 1, 2013

Respectfully submitted,

/Heather Morehouse Ettinger/

Heather Morehouse Ettinger
Registration No.: 51658
Troutman Sanders LLP
The Chrysler Building
405 Lexington Avenue
New York, New York 10174
Direct Tel: (212) 704-6136
Fax: (212) 704-6288
Direct E-mail:
heather.ettinger@troutmansanders.com
Attorneys/Agents for Applicant

PTO/AIA/14 (03-13)
Approved for use through 01/31/2014. OMB 0651-0032
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	244168.000015US4
	Application Number	
Title of Invention	COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING	

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

Secrecy Order 37 CFR 5.2

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

Inventor Information:

Inventor 1 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Fabio		TRENTO	

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

City	Pare, Como	Country of Residence i	IT

Mailing Address of Inventor:

Address 1	Via Alla Valle 20B		
Address 2			
City	Pare, Como	**State/Province**	
Postal Code	I-22020	**Country** i	IT

Inventor 2 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Sergio		CANTOREGGI	

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

City	Cagiallo	Country of Residence i	CH

Mailing Address of Inventor:

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

Inventor 3 Remove

Legal Name

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	244168.000015US4
	Application Number	
Title of Invention	COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING	

Prefix	Given Name	Middle Name	Family Name	Suffix
	Giorgia		ROSSI	

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

City	Cernobbio, Como	Country of Residence i	IT

Mailing Address of Inventor:

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

Inventor 4 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Roberta		CANNELLA	

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

City	Varese	Country of Residence i	IT

Mailing Address of Inventor:

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

Inventor 5 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Daniele		BONADEO	

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

City	Casalzuigno, Varese	Country of Residence i	IT

Mailing Address of Inventor:

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

PTO/AIA/14 (03-13)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	244168.000015US4
	Application Number	
Title of Invention	COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING	

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

Correspondence Information:

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

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

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

Application Information:

Title of the Invention	COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING		
Attorney Docket Number	244168.000015US4	**Small Entity Status Claimed**	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	5	**Suggested Figure for Publication (if any)**	

Publication Information:

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

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

Representative Information:

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

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

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, or 365(c) or indicate National Stage entry from a PCT application. Providing this information in the application data sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	244168.000015US4
	Application Number	
Title of Invention	COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING	

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	Continuation of	13077462	2011-03-31
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
13077462	Continuation of	PCT/IB2010/003106	2010-11-18
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
PCT/IB2010/003106	non provisional of	61262470	2009-11-18
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
PCT/IB2010/003106	non provisional of	61382709	2010-09-14

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

Foreign Priority Information:

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

Remove

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

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

PTO/AIA/14 (03-13)
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	244168.000015US4
	Application Number	
Title of Invention	COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING	

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

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

Authorization to Permit Access:

☒ Authorization to Permit Access to the Instant Application by the Participating Offices

If checked, the undersigned hereby grants the USPTO authority to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the World Intellectual Property Office (WIPO), and any other intellectual property offices in which a foreign application claiming priority to the instant patent application is filed access to the instant patent application. See 37 CFR 1.14(c) and (h). This box should not be checked if the applicant does not wish the EPO, JPO, KIPO, WIPO, or other intellectual property office in which a foreign application claiming priority to the instant patent application is filed to have access to the instant patent application.

In accordance with 37 CFR 1.14(h)(3), access will be provided to a copy of the instant patent application with respect to: 1) the instant patent application-as-filed; 2) any foreign application to which the instant patent application claims priority under 35 U.S.C. 119(a)-(d) if a copy of the foreign application that satisfies the certified copy requirement of 37 CFR 1.55 has been filed in the instant patent application; and 3) any U.S. application-as-filed from which benefit is sought in the instant patent application.

In accordance with 37 CFR 1.14(c), access may be provided to information concerning the date of filing this Authorization.

Applicant Information:

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

PTO/AIA/14 (03-13)
Approved for use through 01/31/2014. OMB 0651-0032
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	244168.000015US4
	Application Number	
Title of Invention	COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING	

Applicant 1 Remove

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

Clear

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

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

Name of the Deceased or Legally Incapacitated Inventor :

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

Organization Name	Helsinn Healthcare S.A.		
Mailing Address Information:			
Address 1	Via Pian Scairolo 9		
Address 2			
City	Lugano/Pazzallo	**State/Province**	
Country [i]	CH	Postal Code	6912
Phone Number		Fax Number	
Email Address			

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

Assignee Information including Non-Applicant Assignee Information:

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

Assignee 1

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

Remove

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

PTO/AIA/14 (03-13)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	244168.000015US4
	Application Number	
Title of Invention	COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING	

Organization Name	Helsinn Healthcare S.A.		
Mailing Address Information:			
Address 1			
Address 2			
City		**State/Province**	
Country i		Postal Code	
Phone Number		Fax Number	
Email Address			

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

Signature:

Remove

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

Signature	/Heather Morehouse Ettinger/			Date (YYYY-MM-DD)	2013-11-01
First Name	Heather Morehouse	Last Name	Ettinger	Registration Number	51658

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

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

Privacy Act Statement

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

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

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

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

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

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

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

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

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

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

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

Electronic Acknowledgement Receipt

EFS ID:	17294241
Application Number:	14069927
International Application Number:	
Confirmation Number:	3207
Title of Invention:	COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING
First Named Inventor/Applicant Name:	Fabio TRENTO
Customer Number:	6980
Filer:	Katherine Harihar/Angelina Stantini
Filer Authorized By:	Katherine Harihar
Attorney Docket Number:	244168.000015.US.4
Receipt Date:	01-NOV-2013
Filing Date:	
Time Stamp:	15:54:42
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal of New Application	US4-PTO-TRANSMITTAL.PDF	149017 13ffdaadd105e6d3c74fa513a077118d88bab6c3	no	2

Warnings:	
Information:	

2		US3-PTO-SPECIFICATION.PDF	2887980 4490701d888dbfa29e06a7ba888fbdef12c1f8ea	yes	36

Multipart Description/PDF files in .zip description		
Document Description	**Start**	**End**
Specification	1	28
Claims	29	35
Abstract	36	36

Warnings:

Information:

3	Drawings-only black and white line drawings	US3-PTO-DRAWINGS.PDF	284419 869c4c7840da9dc1a2abea68bfd2b2b386182791	no	5

Warnings:

Information:

4		US4-PTO-PRELIM.PDF	62198 ca036b313b848d4ff5d185888463bdb74733c03c	yes	3

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

Warnings:

Information:

5	Application Data Sheet	US4-PTO-ADS.PDF	1505980 1feeb04a6dfed1a81c8397653c856b669e7646b6	no	8

Warnings:

Information:

Total Files Size (in bytes):	4889594

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

New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
14/069,927	11/01/2013	1629	0.00	244168.000015US4	51	5

CONFIRMATION NO. 3207

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

FILING RECEIPT

OC00000065051726

Date Mailed: 11/25/2013

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

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

Applicant(s)

Helsinn Healthcare S.A., Lugano/Pazzallo, SWITZERLAND

Assignment For Published Patent Application

Helsinn Healthcare S.A., Lugano/Pazzallo, SWITZERLAND

Power of Attorney: None

Domestic Priority data as claimed by applicant

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

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

Permission to Access - A proper **Authorization to Permit Access to Application by Participating Offices** (PTO/SB/39 or its equivalent) has been received by the USPTO.

If Required, Foreign Filing License Granted: 11/18/2013

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 14/069,927**

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

Non-Publication Request: No

Early Publication Request: No

Title

COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING

Preliminary Class

514

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

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

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

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

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

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

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

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Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

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

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

NOT GRANTED

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

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

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
14/069,927	11/01/2013	Fabio TRENTO	244168.000015US4

CONFIRMATION NO. 3207

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

FORMALITIES LETTER

OC000000065051727

Date Mailed: 11/25/2013

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

Filing Date Granted

Items Required To Avoid Abandonment:

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

- The statutory basic filing fee is missing.
  *Applicant must submit $**280** to complete the basic filing fee for an undiscounted entity. If appropriate, applicant may make a written assertion of entitlement to small entity status and pay the small entity filing fee (37 CFR 1.27) or make a certification of entitlement to micro entity status and pay the micro entity filing fee (37 CFR 1.29).*

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

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

- A substitute specification in compliance with 37 CFR 1.52, 1.121(b)(3), and 1.125, is required. The substitute specification must be submitted with markings and be accompanied by a clean version (without markings) as set forth in 37 CFR 1.125(c) and a statement that the substitute specification contains no new matter (see 37 CFR 1.125(b)). The specification, claims, and/or abstract page(s) submitted is not acceptable and cannot be scanned or properly stored because:
  - The line spacing on the specification, claims, and/or abstract is not 1½ or double spaced (see 37 CFR 1.52(b)).

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

The applicant needs to satisfy supplemental fees problems indicated below.

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

- Additional claim fees of $ **4500** as an undiscounted entity, including any required multiple dependent claim fee, are required. Applicant must submit the additional claim fees or cancel the additional claims for which fees are due.
- A surcharge (for late submission of the basic filing fee, search fee, examination fee or inventor's oath or declaration) as set forth in 37 CFR 1.16(f) of $ **140** for an undiscounted entity, must be submitted.

SUMMARY OF FEES DUE:

Total fee(s) required within **TWO MONTHS** from the date of this Notice is $ **6240** for an undiscounted entity

- $ **280** Statutory basic filing fee.
- $ **140** Surcharge.
- The application search fee has not been paid. Applicant must submit $ **600** to complete the search fee.
- The application examination fee has not been paid. Applicant must submit $ **720** to complete the examination fee for an undiscounted entity.
- Total additional claim fee(s) for this application is $ **4500**
  - $ **840** for **2** independent claims over 3.
  - $ **2880** for **36** total claims over 20.
  - $ **780** for multiple dependent claim surcharge.

Items Required To Avoid Processing Delays:

Applicant is notified that the above-identified application contains the deficiencies noted below. No period for reply is set forth in this notice for correction of these deficiencies. However, if a deficiency relates to the inventor's oath or declaration, the applicant must file an oath or declaration in compliance with 37 CFR 1.63, or a substitute statement in compliance with 37 CFR 1.64, executed by or with respect to each actual inventor no later than the expiration of the time period set in the "Notice of Allowability" to avoid abandonment. See 37 CFR 1.53(f).

- A properly executed inventor's oath or declaration has not been received for the following inventor(s):
  Fabio TRENTO
  Sergio CANTOREGGI
  Giorgia ROSSI
  Roberta CANNELLA
  Daniele BONADEO

  Applicant may submit the inventor's oath or declaration at any time before the Notice of Allowance and Fee(s) Due, PTOL-85, is mailed.

Replies must be received in the USPTO within the set time period or must include a proper Certificate of Mailing or Transmission under 37 CFR 1.8 with a mailing or transmission date within the set time period. For more information and a suggested format, see Form PTO/SB/92 and MPEP 512.

Replies should be mailed to:

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

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

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

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

/fberhane/

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

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 14/069,927

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	280
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	600
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	720
TOTAL CLAIMS (37 CFR 1.16(i))	56 minus 20 =	* 36			OR	x 80 =	2880
INDEPENDENT CLAIMS (37 CFR 1.16(h))	5 minus 3 =	* 2				x 420 =	840
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						0.00
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							780
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	6100

APPLICATION AS AMENDED - PART II

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

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

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

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

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

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

MULTIPLE DEPENDENT CLAIM FEE CALCULATION SHEET

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

Application Number	Filing Date
14069927	

Applicant(s) Fabio TRENTO

* May be used for additional claims or amendments

CLAIMS	AS FILED		AFTER FIRST AMENDMENT		AFTER SECOND AMENDMENT	
	Indep	Depend	Indep	Depend	Indep	Depend
1	1					
2		1				
3		2				
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7		(1)				
8		(1)				
9		(1)				
10		(1)				
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14		(1)				
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44		2				
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48		(1)				
49		(1)				
50		(1)				
Total Indep	5		0		0	
Total Depend	51	↵	0	↵	0	↵
Total Claims	56		0		0	

CLAIMS	*		*		*	
	Indep	Depend	Indep	Depend	Indep	Depend
51		(1)				
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Docket No.: 244168.000015US4
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Fabio TRENTO et al.	Customer No.: 06980
Application No.: 14/069,927	Confirmation No.: 3207
Filing Date: November 1, 2013	Art Unit: 1629
For: COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING	Examiner: Not yet assigned

RESPONSE TO NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

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

Dear Sir:

In response to the Notice to File Missing Parts of Nonprovisional Application dated November 25, 2013, submitted herewith are the following for filing in the above-referenced application:

1. Late surcharge, $140;
2. Statutory basic filing fee, $280;
3. Application search fee, $600;
4. Application examination fee, $720;
5. Second Preliminary Amendment, together with substitute specification and amended claims;
6. Petition for Extension of Time and required fee, $600.

Please charge Deposit Account No. 20-1507 of Customer No. 06980 in the amount of $2340. Please charge any shortage in fees due in connection with the filing of this paper to Deposit Account No. 20-1507 and please credit any excess fees to such deposit account.

Dated: March 21, 2014

Respectfully submitted,

/kharihar/
Katherine Harihar, Reg. No. 71140, for
Heather Morehouse Ettinger
Registration No. 51658
Troutman Sanders LLP
The Chrysler Building
405 Lexington Avenue
New York, New York 10174
Direct Tel: (212) 704-6136
Fax: (212) 704-6288
heather.ettinger@troutmansanders.com
Attorneys/Agents for Applicants

Docket No.: 244168.000015US4
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Fabio TRENTO et al.	Customer No.: 06980
Application No.: 14/069,927	Confirmation No.: 3207
Filing Date: November 1, 2013	Art Unit: 1629
For: COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING	Examiner: Not yet assigned

SECOND PRELIMINARY AMENDMENT

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

Dear Sir:

INTRODUCTORY COMMENTS

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

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

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

Remarks begin on page 6 of this paper.

AMENDMENTS TO THE SPECIFICATION

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

AMENDMENTS TO THE CLAIMS

The following listing of claims replaces all prior listings:

Listing of claims

Claims 1 – 51. (Cancelled)

52) (New) A method of treating chemotherapy induced nausea and vomiting (CINV) comprising administering to a subject receiving chemotherapy a regimen of palonosetron, netupitant and dexamethasone.

53) (New) A method of treating chemotherapy induced nausea and vomiting (CINV) in a subject receiving chemotherapy comprising administering to a subject receiving chemotherapy a regimen of netupitant and a sub-therapeutic dose of dexamethasone.

54) (New) The method of claim 53, wherein the sub-therapeutic dose of dexamethasone comprises from about 50 to 70% of a minimum effective dose when administered alone against CINV.

55) (New) A method of treating chemotherapy induced nausea and vomiting (CINV) comprising inducing in a subject receiving chemotherapy blood levels of palonosetron and netupitant effective to treat said CINV.

56) (New) The method of claim 52, wherein the chemotherapy comprises moderately or highly emetogenic chemotherapy.

57) (New) The method of claim 52, wherein said chemotherapy comprises carboplatin.

58) (New) The method of claim 52, wherein the netupitant and palonosetron are administered no more than one hour prior to administration of the chemotherapy.

59) (New) The method of claim 52, wherein when said chemotherapy is highly emetic chemotherapy, the chemotherapy is selected from the group consisting of carmustine, cisplatin, cyclophosphamide ≧1500 mg/m^2, dacarbazine, dactinomycin, mechlorethamine, streptozotocin and combinations thereof.

60) (New) The method of claim 52, wherein when said chemotherapy is moderately emetic chemotherapy, the chemotherapy is selected from the group consisting of carboplatin, cyclophosphamide <1500 mg/m^2, cytarabine >1 mg/m^2, daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, oxaliplatin and combinations thereof.

61) (New) The method of claim 52, wherein said chemotherapy is selected from the group consisting of carboplatin, cyclophosphamide, cytarabine >1 mg/m^2, daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, carmustine, cisplatin, dacarbazine, dactinomycin, mechlorethamine, streptozotocin, oxaliplatin and combinations thereof.

62) (New) The method of claim 53, wherein when said chemotherapy is highly emetic chemotherapy, the chemotherapy is selected from the group consisting of carmustine, cisplatin, cyclophosphamide ≧1500 mg/m^2, dacarbazine, dactinomycin, mechlorethamine, streptozotocin and combinations thereof.

63) (New) The method of claim 53, wherein when said chemotherapy is moderately emetic chemotherapy, the chemotherapy is selected from the group consisting of carboplatin, cyclophosphamide <1500 mg/m^2, cytarabine >1 mg/m^2, daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, oxaliplatin and combinations thereof.

64) (New) The method of claim 53, wherein said chemotherapy is selected from the group consisting of carboplatin, cyclophosphamide, cytarabine >1 mg/m^2, daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, carmustine, cisplatin, dacarbazine, dactinomycin, mechlorethamine, streptozotocin, oxaliplatin and combinations thereof.

65) (New) The method of claim 55, wherein when said chemotherapy is highly emetic chemotherapy, the chemotherapy is selected from the group consisting of carmustine, cisplatin, cyclophosphamide ≧1500 mg/m^2, dacarbazine, dactinomycin, mechlorethamine, streptozotocin and combinations thereof.

66) (New) The method of claim 55, wherein when said chemotherapy is moderately emetic chemotherapy, the chemotherapy is selected from the group consisting of carboplatin, cyclophosphamide <1500 mg/m^2, cytarabine >1 mg/m^2, daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, oxaliplatin and combinations thereof.

67) (New) The method of claim 55, wherein said chemotherapy is selected from the group consisting of carboplatin, cyclophosphamide, cytarabine >1 mg/m^2, daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, carmustine, cisplatin, dacarbazine, dactinomycin, mechlorethamine, streptozotocin, oxaliplatin and combinations thereof.

REMARKS

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

Claims 1-51 were pending in the application as filed. In the present Second Preliminary Amendment, claims 1-51 are cancelled without prejudice or disclaimer and claims 52-67 have been added. Support for the newly added claims can be found throughout the originally filed claims and specification. No new matter is added by this amendment.

Applicant reserves the right to pursue cancelled or removed subject matter in a continuation/divisional application.

Early and favorable examination is requested.

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

Dated: March 21, 2014

Respectfully submitted,

/kharihar/
Katherine Harihar, Reg. No. 71140, for
Heather Morehouse Ettinger
Registration No.: 51658
Troutman Sanders LLP
The Chrysler Building
405 Lexington Avenue
New York, New York 10174
Direct Tel: (212) 704-6136
Fax: (212) 704-6288
Direct E-mail:
heather.ettinger@troutmansanders.com
Attorneys/Agents for Applicant

COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING

CROSS-REFERENCE TO RELATED APPLICATIONS

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

FIELD OF THE INVENTION

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

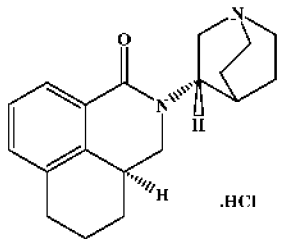
BACKGROUND OF THE INVENTION

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

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

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

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

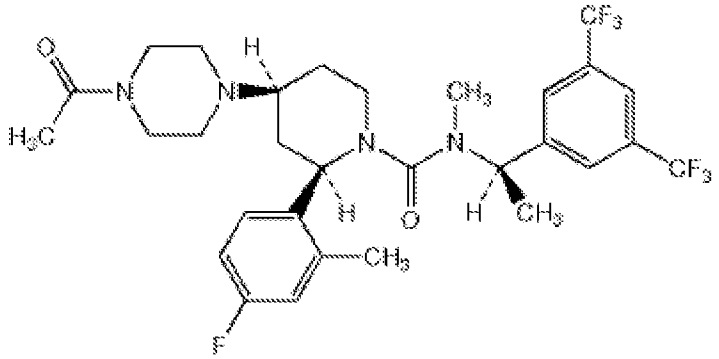


Methods of synthesizing palonosetron are described in U.S. Patent Nos. 5,202,333 and 5,510,486. Pharmaceutically acceptably dosage forms are described in PCT publications WO 2004/067005 and WO 2008/049552 from Helsinn Healthcare.

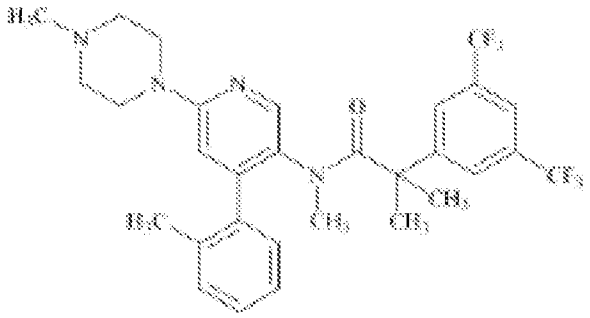
NK_1 antagonists have also recently emerged as a tool for combating nausea and vomiting from emetogenic medical procedures. Most recently, aprepitant was approved by the Food and Drug Administration ("FDA") for use in combination with other anti-emetic agents for the prevention of nausea and vomiting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

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

its effects have been inconsistent. Casopitant is another NK_1 antagonist that has been tested against nausea and vomiting in humans. A clinical study of casopitant is discussed in *Therapeutics and Clinical Risk Management* 2009:5 pp375-384 to Ruhlmann et al. and *Drug Metabolism and Disposition,* vol.37, No. 8, 2009, pp.1635-1645 to Pellegatti et al. As reported by Ruhlmann *et al.* in THERAPEUTICS AND CLINICAL RISK MANAGEMENT, 2009:5 375-384, casopitant had no statistically significant effect against nausea when administered in response to moderately emetogenic chemotherapy, and even induced nausea as a side effect. Casopitant has the formula (2*R*,4*S*)-4-(4-acetytlpiperazin-l-y1)-*N*-{(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethy1}-2-(4-fluoro-2-methylpheny1)-*N*-methylpiperidine-l-carboxamide, and the below chemical structure:



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



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

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

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

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

OBJECTS OF THE INVENTION

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

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

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

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

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

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

SUMMARY OF THE INVENTION

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

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

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

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

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

~~and palonosetron, wherein said first dose comprises from 50 to 70% of a minimum effective dose when administered alone; and~~

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

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

- Day 1 palonosetron -- administering to said patient on day one a therapeutically effective amount of a $5\text{-}HT_3$ antagonist (preferably palonosetron) effective to treat said nausea and vomiting during the acute and delayed phases;

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

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

The dosage forms are extremely versatile and stable owing to their unique design and formulation. This versatility and stability is accomplished by formulating the NK1 antagonist and palonosetron in separate dosage forms and combining the dosage forms in one capsule. Thus, for example, the palonosetron can be formulated in a small gel-cap at a dose of around 0.5 mg, and the netupitant or other NK1 antagonist formulated in a tablet at a dose of about 100 to 150 mg. A

capsule can then be filled with one or more palonosetron gel-caps and one or more netupitant (or other NK1 antagonist) tablets, depending on the therapeutic objective for the product. Because the palonosetron and NK1 antagonist are in separate dosage units, they can be formulated without regard to the stability of the other, and without degradation to by-products, for instance (3S)-3-[(3aS)-1-oxo- 2,3,3a,4,5,6-hexahydro-1*H*-benzo[*de*] isoquinoline-2-y1]-1-azoniabicyclo[2.2.2]octan-1-olate, a degradation by-product of palonosetron. As a result, the presently discovered dosage forms offer advantages, such as, reducing drug-drug interaction, improving stability, and potentiating effects of each component of the dosage forms in treating or preventing emesis.

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

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

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

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

BRIEF DESCRIPTION OF THE DRAWINGS

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

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

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

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

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

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

DETAILED DESCRIPTION OF THE INVENTION

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

Definitions and Use of Terms

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

When used herein the term "about" or "ca." will compensate for variability allowed for in the pharmaceutical industry and inherent in pharmaceutical products, such as differences in product strength and bioavailability due to manufacturing variations and time-induced product degradation.

The term allows for any variation which in the practice of pharmaceuticals would allow the product being evaluated to be considered pharmaceutically equivalent or bioequivalent, or both if the context requires, to the recited strength of a claimed product.

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

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

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

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

The minimum effective dose of dexamethasone, when used to treat CINV induced by highly emetogenic chemotherapy, has been demonstrated to be 20 mg. administered orally or by

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

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

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

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

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

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

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

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

Methods of Treatment

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

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

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

~~(i) administering to said patient on day one netupitant or a pharmaceutically acceptable salt thereof, in an amount which is therapeutically effective to treat nausea and vomiting during the~~

~~acute and delayed phases, which enters the systemic circulation, crosses the blood brain barrier and occupies at least 70% of NK_1 receptors in the striatum seventy-two hours after said administration;~~

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

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

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

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

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

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

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

Various sub-embodiments are envisaged for these principal embodiments. For example, the netupitant can be administered as a free base or a pharmaceutically acceptable salt thereof, but is preferably administered as the free base. In addition, the netupitant is preferably administered in an

amount ranging from about 50 to about 500 mg., from about 200 to about 400 mg., and preferably about 300 mg., based on the weight of the free base. A preferred route of administration for the netupitant is oral. In terms of binding to NK_1 receptors, the netupitant preferably binds to at least 80 or even 85% of NK_1 receptors in the striatum seventy-two hours after administration. As of ninety six hours after administration, the netupitant preferably binds less than 70, 60, 50 or even 40% of said NK_1 receptors.

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

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

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

Pharmaceutical Compositions

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

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

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

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

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

Combined Oral Dosage Forms

As discussed above, the invention provides versatile combined oral dosage forms of palonosetron and an NK1 antagonist that can be readily modified depending on the therapeutic objective, and that do not present issues of stability and degradation. In a preferred embodiment, the

invention provides a capsule for oral administration made from a hard outer shell that houses one or more NK1 antagonist tablets and one or more palonosetron soft-gel capsules. The finished capsule and the tablet(s) and soft-gel capsule(s) housed within the capsule shell are all preferably formulated as immediate release dosage forms. Netupitant and casopitant, and their pharmaceutically acceptable salts, are particularly preferred NK_1 antagonists for the combined oral dosage forms of this invention.

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

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

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

Hard Outer Shell

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

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

Soft-Gel Capsule

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

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

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

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

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

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

Tablet

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

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

Application of The Combined Oral Dosage Forms

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

EXAMPLES

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

EXAMPLE 1 — PREPARATION OF ORAL DOSAGE FORM

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

TABLE 1: REPRESENTATIVE SOFT-GEL FORMULATION

Ingredient	Approximate Amount (mg/Capsule)	Function
Fill Solution		
Palonosetron HC1	0.56[1]	Active

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

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

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

TABLE 2: REPRESENTATIVE TABLET FORMULATION

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

EXAMPLE 2 — PHARMACOKINETICS OF COMBINED DOSAGE FORM

Objective

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

Methods

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

The following treatments were investigated:

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

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

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

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

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

Results

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

Table 3: Summary of Netupitant Pharmacokinetic Parameters

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

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

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

Table 4: Summary of Palonosetron Pharmacokinetic Parameters

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

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

EXAMPLE 3: NETUPITANT + DEXAMETHASONE DRUG INTERACTION STUDY

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

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

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

EXAMPLE 4: NETUPITANT PET RECEPTOR OCCUPANCY STUDY

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

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

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

EXAMPLE 5: CLINICAL EFFICACY STUDY

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

medication; No emesis. These endpoints were evaluated for the 0-120 hour interval (overall), acute and delayed phase.

- Time to first emetic episode, Time to first rescue medication, Time to treatment failure (based on time to the first emetic episode or time to the first rescue medication, whichever occurs first);
- Severity of nausea for the overall, acute and delayed phase; • Patient global satisfaction with anti-emetic therapy by means of VAS for each 24 hour interval.

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

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

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

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

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

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

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

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

EXAMPLE 7: COMPARATIVE RESULTS OF APREPITANT DOSING REGIMEN

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

TABLE 7

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

TABLE 8

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

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

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

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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.

COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING

CROSS-REFERENCE TO RELATED APPLICATIONS

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

FIELD OF THE INVENTION

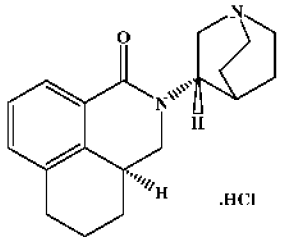
The present invention relates to the use of centrally acting NK_1 antagonists to treat nausea and vomiting, particular nausea and vomiting induced by highly emetogenic chemotherapy, and to the treatment of such nausea and vomiting over multiple consecutive days. The present invention also relates to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

BACKGROUND OF THE INVENTION

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

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

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

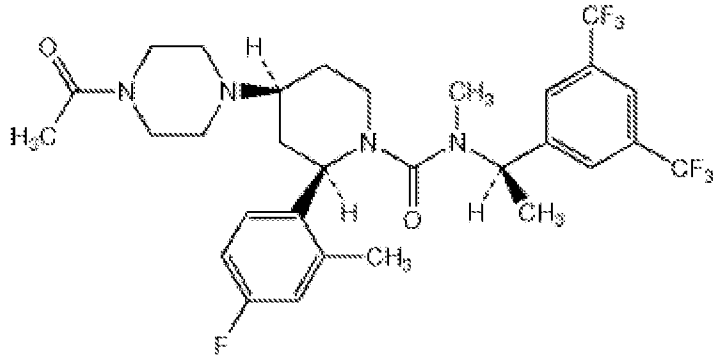


Methods of synthesizing palonosetron are described in U.S. Patent Nos. 5,202,333 and 5,510,486. Pharmaceutically acceptably dosage forms are described in PCT publications WO 2004/067005 and WO 2008/049552 from Helsinn Healthcare.

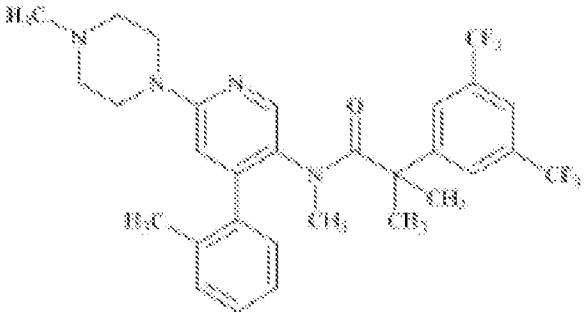
NK_1 antagonists have also recently emerged as a tool for combating nausea and vomiting from emetogenic medical procedures. Most recently, aprepitant was approved by the Food and Drug Administration ("FDA") for use in combination with other anti-emetic agents for the prevention of nausea and vomiting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

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

effect against nausea, its effects have been inconsistent. Casopitant is another NK_1 antagonist that has been tested against nausea and vomiting in humans. A clinical study of casopitant is discussed in *Therapeutics and Clinical Risk Management* 2009:5 pp375-384 to Ruhlmann et al. and *Drug Metabolism and Disposition,* vol.37, No. 8, 2009, pp.1635-1645 to Pellegatti et al. As reported by Ruhlmann *et al.* in THERAPEUTICS AND CLINICAL RISK MANAGEMENT, 2009:5 375-384, casopitant had no statistically significant effect against nausea when administered in response to moderately emetogenic chemotherapy, and even induced nausea as a side effect. Casopitant has the formula (2*R*,4*S*)-4-(4-acetytlpiperazin-l-y1)-*N*-{(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethy1}-2-(4-fluoro-2-methylpheny1)-*N*-methylpiperidine-l-carboxamide, and the below chemical structure:



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



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

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

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

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

OBJECTS OF THE INVENTION

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

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

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

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

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

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

SUMMARY OF THE INVENTION

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

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

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

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

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

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

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

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

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

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

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

BRIEF DESCRIPTION OF THE DRAWINGS

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

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

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

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

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

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

DETAILED DESCRIPTION OF THE INVENTION

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

Definitions and Use of Terms

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

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

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

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

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

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

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

dexamethasone is 20 mg. administered orally or by injection on day one, and zero mg. on days two, three and four.

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

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

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

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

"Moderately emetogenic chemotherapy" refers to chemotherapy having a moderate degree of emetogenic potential, and includes chemotherapy based on carboplatin,

cyclophosphamide < 1500 mg/m^2, cytarabine > 1 mg/m^2, daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, and oxaliplatin.

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

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

Methods of Treatment

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

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

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

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

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

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

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

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

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

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

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

Pharmaceutical Compositions

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

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

Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition.

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

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

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

Combined Oral Dosage Forms

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

formulated as immediate release dosage forms. Netupitant and casopitant, and their pharmaceutically acceptable salts, are particularly preferred NK_1 antagonists for the combined oral dosage forms of this invention.

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

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

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

Hard Outer Shell

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

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

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

Soft-Gel Capsule

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

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

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

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

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

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

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

Tablet

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

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

Application of The Combined Oral Dosage Forms

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

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

EXAMPLES

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

EXAMPLE 1 — PREPARATION OF ORAL DOSAGE FORM

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

TABLE 1: REPRESENTATIVE SOFT-GEL FORMULATION

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

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

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

TABLE 2: REPRESENTATIVE TABLET FORMULATION

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

EXAMPLE 2 — PHARMACOKINETICS OF COMBINED DOSAGE FORM

Objective

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

Methods

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

The following treatments were investigated:

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

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

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

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

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

Results

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

maximum plasma concentration was observed (t_{max}). Results are depicted in below Tables 3 and 4, as well as Figures 2 and 3.

Table 3: Summary of Netupitant Pharmacokinetic Parameters

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

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

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

Table 4: Summary of Palonosetron Pharmacokinetic Parameters

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

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

EXAMPLE 3: NETUPITANT + DEXAMETHASONE DRUG INTERACTION STUDY

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

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

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

EXAMPLE 4: NETUPITANT PET RECEPTOR OCCUPANCY STUDY

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

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

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

groups (100 mg., 300 mg. and 450 mg) showed a consistent but small increase in NK_1-RO_s with increasing netupitant dose. (Figure 5)

EXAMPLE 5: CLINICAL EFFICACY STUDY

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

EXAMPLE 7: COMPARATIVE RESULTS OF APREPITANT DOSING REGIMEN

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

TABLE 7

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

TABLE 8

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

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

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

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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.

Electronic Patent Application Fee Transmittal

Application Number:	14069927
Filing Date:	01-Nov-2013
Title of Invention:	COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING
First Named Inventor/Applicant Name:	Fabio TRENTO
Filer:	Katherine Harihar
Attorney Docket Number:	244168.000015US4

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Utility application filing	1011	1	280	280
Utility Search Fee	1111	1	600	600
Utility Examination Fee	1311	1	720	720
Pages:				
Claims:				
Miscellaneous-Filing:				
Late Filing Fee for Oath or Declaration	1051	1	140	140
Petition:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 2 months with $0 paid	1252	1	600	600
Miscellaneous:				
		Total in USD ($)		**2340**

Electronic Acknowledgement Receipt

EFS ID:	18554190
Application Number:	14069927
International Application Number:	
Confirmation Number:	3207
Title of Invention:	COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING
First Named Inventor/Applicant Name:	Fabio TRENTO
Customer Number:	6980
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Warnings:					
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Document Description	Start	End
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Specification	2	2
Claims	3	5
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4	Specification	US-PTO-MARKEDSPEC.PDF	301094 5f8b1f368b3ded5229bf72228ace37ece4eef32e	no	28
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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.

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PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)	Docket Number (Optional) 244168.000015US4
Application Number 14/069,927; Conf. No. 3207	Filed 11-01-2013
For COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING	
Art Unit 1629	Examiner Not yet assigned

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above-identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

		Fee	Small Entity Fee	Micro Entity Fee	
☐	One month (37 CFR 1.17(a)(1))	$200	$100	$50	$
☑	Two months (37 CFR 1.17(a)(2))	$600	$300	$150	$ 600
☐	Three months (37 CFR 1.17(a)(3))	$1,400	$700	$350	$
☐	Four months (37 CFR 1.17(a)(4))	$2,200	$1,100	$550	$
☐	Five months (37 CFR 1.17(a)(5))	$3,000	$1,500	$750	$

☐ Applicant asserts small entity status. See 37 CFR 1.27.

☐ Applicant certifies micro entity status. See 37 CFR 1.29.
Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously.

☐ A check in the amount of the fee is enclosed.

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

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

☑ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 201507.

☑ Payment made via EFS-Web.

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.

I am the

☐ applicant.

☐ attorney or agent of record. Registration number _____.

☑ attorney or agent acting under 37 CFR 1.34. Registration number 51658.

/kharihar/ Katherine Harihar, Reg. 71140, for	March 21, 2014
Signature	Date
Heather Morehouse Ettinger	212-704-6136
Typed or printed name	Telephone Number

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.

☐ * Total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.136(a). 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 6 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: Mail Stop PCT, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Privacy Act Statement

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

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

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 14/069,927	Filing Date 11/01/2013	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT **03/21/2014**

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 16	Minus	** 20	= 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

AMENDMENT

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

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

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

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

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

LIE
/FELICIA R. FARMER/

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

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

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
14/069,927	11/01/2013	Fabio TRENTO	244168.000015US4

CONFIRMATION NO. 3207

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

NOTICE

OC00000067336072

Date Mailed: 04/01/2014

INFORMATIONAL NOTICE TO APPLICANT

Applicant is notified that the above-identified application contains the deficiencies noted below. No period for reply is set forth in this notice for correction of these deficiencies. However, if a deficiency relates to the inventor's oath or declaration, the applicant must file an oath or declaration in compliance with 37 CFR 1.63, or a substitute statement in compliance with 37 CFR 1.64, executed by or with respect to each actual inventor no later than the expiration of the time period set in the "Notice of Allowability" to avoid abandonment. See 37 CFR 1.53(f).

The item(s) indicated below are also required and should be submitted with any reply to this notice to avoid further processing delays.

- A properly executed inventor's oath or declaration has not been received for the following inventor(s):
  Fabio TRENTO
  Sergio CANTOREGGI
  Giorgia ROSSI
  Roberta CANNELLA
  Daniele BONADEO

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 14/069,927

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	280
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	600
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	720
TOTAL CLAIMS (37 CFR 1.16(i))	16 minus 20 =	*			OR	x 80 =	0.00
INDEPENDENT CLAIMS (37 CFR 1.16(h))	3 minus 3 =	*				x 420 =	0.00
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						0.00
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0.00
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	1600

APPLICATION AS AMENDED - PART II

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

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

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

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

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

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

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
14/069,927	11/01/2013	1629	1740	244168.000015US4	16	3

CONFIRMATION NO. 3207

UPDATED FILING RECEIPT

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

OC000000067336071

Date Mailed: 04/01/2014

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

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

Applicant(s)

Helsinn Healthcare S.A., Lugano/Pazzallo, SWITZERLAND

Assignment For Published Patent Application

Helsinn Healthcare S.A., Lugano/Pazzallo, SWITZERLAND

Power of Attorney: None

Domestic Priority data as claimed by applicant

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

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

Permission to Access - A proper **Authorization to Permit Access to Application by Participating Offices** (PTO/SB/39 or its equivalent) has been received by the USPTO.

If Required, Foreign Filing License Granted: 11/18/2013

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 14/069,927**

Projected Publication Date: 07/10/2014

Non-Publication Request: No

Early Publication Request: No

Title

COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING

Preliminary Class

514

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

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

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

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

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

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

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

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

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

NOT GRANTED

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

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The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The U.S. offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to promote and facilitate business investment. SelectUSA provides information assistance to the international investor community; serves as an ombudsman for existing and potential investors; advocates on behalf of U.S. cities, states, and regions competing for global investment; and counsels U.S. economic development organizations on investment attraction best practices. To learn more about why the United States is the best country in the world to develop technology, manufacture products, deliver services, and grow your business, visit http://www.SelectUSA.gov or call +1-202-482-6800.

Substitute for form 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	14/069,927
				Filing Date	2013-11-01
				First Named Inventor	Fabio TRENTO
				Art Unit	1612
(Use as many sheets as necessary)				Examiner Name	Unassigned
Sheet	1	of	2	Attorney Docket Number	244168.000015US4

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Patent/ Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	A1	5202333	4/13/1993	Berger et al.	
	A2	5510486	4/23/1996	Robinson, III et al.	
	A3	6297375	10/2/2001	Bos et al.	
	A4	6719996	4/13/2004	Kuentz et al.	
	A5	6593472	7/15/2003	Hoffmann et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]
	B1	WO 2008/049552 A 1	2008-05-02	Helsinn Healthcare SA		
	B2	WO 2004/067005 A 1	2004-08-12	Helsinn Healthcare SA		
	B3	WO 2004/073714 A1	2004-09-02	Helsinn Healthcare SA		
	B4	WO 2004/045615 A1	2004-06-03	Helsinn Healthcare SA		

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	C1	Press Release, GSK provides update on regulatory filings for Zunrisa/Rezonic; Issued: Monday 28 September 2009, London UK.	
	C2	WARR et al., Efficacy and tolerability of aprepitant for the prevention of chemotherapy-induced nausea and vomiting in patients with breast cancer after moderately emetogenic chemotherapy. (2005) J. Clin. Oncol. 23(12):2822-2830.	
	C3	HERRINGTON et al., Randomized, placebo-controlled, pilot study evaluating aprepitant single dose plus palonosetron and dexamethasone for the prevention of acute and delayed chemotherapy-induced nausea and vomiting. (2008) Cancer 112(9):2080-2087.	
	C4	YEO et al., A randomized study of aprepitant, ondansetron and dexamethasone for chemotherapy-induced nausea and vomiting in Chinese breast cancer patients receiving moderately emetogenic chemotherapy. (2009) Breast Cancer Res. Treat. 113:529-535.	
	C5	LONGO et al., Palonosetron plus 3-day aprepitant and dexamethasone to prevent nausea and vomiting in patients receiving highly emetogenic chemotherapy. (2011) Support Care Cancer 19:1159-1164.	
	C6	Press Release, NK1 receptor antagonist by Roche; Issued: Thursday, 23 February 2006, http://leaddiscovery.blogspot.com/2006/02/nk1-receptor-antagonist-by-roche.html (leaddiscovery.co.uk)	
	C7	March 27, 2003, Approved FDA Prescribing Information for Emend	

Examiner Signature		Date Considered	

Substitute for form 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	14/069,927
				Filing Date	2013-11-01
				First Named Inventor	Fabio TRENTO
				Art Unit	1612
(Use as many sheets as necessary)				Examiner Name	Unassigned
Sheet	2	of	2	Attorney Docket Number	244168.000015US4

	C8	RUHLMANN, CHRISTINA et al., "Casopitant: a novel NK1-receptor antagonist in the prevention of chemotherapy- induced nausea and vomiting," Therapeutics and Clinical Risk Management, 2009:5 pp. 375-384	
	C9	PELLEGATTI, MARIO et al., "Disposition and Metabolism of Radiolabeled Casopitant in Humans," Drug Metabolism 0 and Disposition, vol. 37, no. 8, 2009, pp.1635-1645	
	C10	HUANG, SHIH-CHUNG et al., "Neurokinin-1 receptor antagonists: a comprehensive patent survey," Expert Opin. Ther. 0 Patents (2010) 20(8), pp. 1019-1045	
	C11	REDDY, G. KESAVA et al., "Novel Neurokinin-1 Antagonists as Antiemetics for the Treatment of Chemotherapy-Induced Emesis," Supportive Cancer Therapy, April 1, 2006, LNKD-PUBMED: 18632487, vol. 3, no. 3, pp. 140-142, XP002626039, ISSN: 1543-2912	
	C12	DE WIT, R., "Current position of 5HT3 antagonists and the additional value of NK1 antagonists; a new class of antiemetics," British Journal of Cancer, June 16, 2003, LNKD-PUBMED: 12799621, vol. 88, no. 12, pp. 1823-1827, XP002626041, ISSN: 0007-0920	
	C13	DIEMUNSCH, P. et al., "Neurokinin-1 receptor antagonists in the prevention of postoperative nausea and vomiting," British Journal of Anaesthesia, July 2009, LNKD-PUBMED: 19454547, vol. 103, no. 1, pp. 7-13, XP002626040, ISSN: 1471-6771	
	C14	DIEMUNSCH, PIERRE et al., "Potential of Substance P Antagonists as Antiemetics," January 1,2003, Antiemetic Therapy, Basel [U.A.]: Karger, CH, pp. 78-97, XP008133831, ISBN: 978-3-8055-7547-8	
	C15	GRUNBERG, STEVEN M., et al., "Effectiveness of a single-day three-drug regimen of dexamethasone, palonosetron, and aprepitant for the prevention of acute and delayed nausea and vomiting caused by moderately emetogenic chemotherapy," Support Care Cancer: Official Journal of the Multinational Association of Supportive Care in Cancer, May 2009 LNKD-PUBMED: 19037667, vol. 17, no. 5, pp. 589-594, XP002626042, ISSN: 1433-7339	
	C16	STATHIS, MARIGO et al., "Inhibition of substance P-mediated responses in NG1 08-15 celis by netupitant and palonosetron exhibit synergistic effects," European Journal of Pharmacology 689 (2012) pp. 25-30	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

Examiner Signature		Date Considered	

Electronic Acknowledgement Receipt

EFS ID:	18888121
Application Number:	14069927
International Application Number:	
Confirmation Number:	3207
Title of Invention:	COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING
First Named Inventor/Applicant Name:	Fabio TRENTO
Customer Number:	6980
Filer:	Katherine Harihar/Angelina Stantini
Filer Authorized By:	Katherine Harihar
Attorney Docket Number:	244168.000015US4
Receipt Date:	29-APR-2014
Filing Date:	01-NOV-2013
Time Stamp:	12:55:59
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	PTO-IDSTRANS-15US4.pdf	82144 1a6215e9de83b5f549440bb84e0892a1467dac38	no	4

Warnings:	
Information:	

2	Information Disclosure Statement (IDS) Form (SB08)	PTO-IDSSB08-15US4.pdf	109291 a41fe55fe202a79ae5119b0a5c1cc92fba7cdfbe	no	2

Warnings:	
Information:	
This is not an USPTO supplied IDS fillable form	
Total Files Size (in bytes):	191435

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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
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Docket No.: 244168.000015US4
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Fabio TRENTO, ET AL.	Customer No.: 06980
Application No.: 14/069,927	Confirmation No.: 3207
Filing Date: November 1, 2013	Art Unit: 1612
For: COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING	Examiner: Unassigned

INFORMATION DISCLOSURE STATEMENT (IDS)

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

Dear Sir:

This Information Disclosure Statement is submitted in accordance with 37 C.F.R. 1.97, 1.98, and it is requested that the information set forth in this statement and in the listed documents be considered during the pendency of the above-identified application, and any other application relying on the filing date of the above-identified application or cross-referencing it as a related application.

1. This IDS should be considered, in accordance with 37 C.F.R. 1.97, as it is filed: (Check one of the boxes A-D)

☐ A. within three months of the filing date of the above-identified national application or within three months of the entry into the national stage of the above identified national application

☒ **B. before the mailing date of a first office action on the merits, or a first office action after filing a request for continued examination.**

☐ C. after (A) and (B) above, but before final rejection or allowance, and Applicant has made the necessary statement in box "i" below or paid the necessary fee in box "ii" below.

(check one of the boxes "i" and "ii" below:)

☐ i. Counsel states that, upon information and belief, each item of information listed herein was (check one of boxes (a) or (b))

☐ (a) 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 this IDS; or

☐ (b) not cited in a communication from a foreign patent office in a counterpart foreign application and, to the knowledge of undersigned after making reasonable inquiry, was not known to any individual designated in 1.56(c) more than three months prior to the filing of this IDS.

☐ ii. Please charge Deposit Account 20-1507 for the fee set forth in 1. 17(p), presently believed to be $180 ($90 for Small Entity).

☐ D. after (A), (B) and (C) above, but before payment of the issue fee: Applicant petitions under 37 C.F.R. 1.97(d) for the consideration of this IDS. Under 37 CFR 1.17(p), please charge Deposit Account 20-1507 the fee of $180.00 ($90.00 for Small Entity). Counsel certifies that, upon information and belief, each item of information listed herein was

(check one of the boxes "a" and "b" below:)

☐ (a) 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 this IDS; or

☐ (b) was not cited in a communication from a foreign patent office in a counterpart foreign application and, to the knowledge of undersigned after making reasonable inquiry, was not known to any individual designated in 1.56(c) more than three months prior to the filing of this IDS.

2. In accordance with 37 C.F.R. 1.98, this IDS includes a list (e.g., form PTO/SB/08) of all patents, publications, or other information submitted for consideration by the office, either incorporated into this IDS or as an attachment hereto. A copy of each document listed is attached, except as explained below.

(check boxes A, B and/or C and fill in blanks, if appropriate.)

[X] **A. Pursuant to the Notice issued by the United States Patent and Trademark Office dated July 11, 2003 waiving the requirements of 37 C.F.R. § 1.98(a)(2)(i), a copy/copies of the United States Patent on PTO/SB08 is/are not being submitted.**

[ ] B. Document(s) _____is (are) deemed substantially cumulative to document(s) _____ , and, in accordance with 1.98(c), only a copy of each of the latter documents is enclosed.

[X] **C. Certain documents were previously cited by or submitted to the Office in the following prior applications, which are relied upon under 35 U.S.C. 120:**

U.S. Application No. 13/077,462 filed March 31, 2011, now U.S. Patent 8,623,826

Applicant identifies these documents by attaching hereto copies of the forms PTO-892, PTO-1449 and/or PTO/SB/08 from the files of the prior application(s) or a fresh PTO/SB/08 listing these documents, and request that they be considered and made of record in accordance with 1.98(d). Per 37 CFR 1.98(d), copies of these documents need not be filed in this application.

[ ] 3. Foreign Patent Document Cite Nos. ___ are not in the English language. In accordance with 1.98(c), Applicant states:

- [ ] An English translation of each document (or of the pertinent portions thereof), or a copy of each corresponding English-language patent or application, or English-language abstract (or claim) is enclosed.
- [ ] The requirement for a concise explanation of the relevance of any foreign language document is satisfied by the attached search report; citation of the documents cited in the search report shall not be construed as an admission that they are or are considered to be, material to patentability of the subject matter claimed herein (See MPEP §609).
- [ ] A concise explanation of the relevance of document(s) _____ is set forth as follows: [Insert concise explanation of relevance]
- [ ] A concise explanation of the relevance of document(s) _____ can be found on page(s) _____ of the specification.
- [ ] A concise explanation of document(s) _____ can be found on the attached sheet.

[x] 4. **No explanation of relevance is necessary for documents in the English language (see reply to Comments 67 in the preamble to the final rules; 1135 OG 13 at 20).**

[ ] 5. Other information being provided for the examiner's consideration follows:

6. In accordance with 37 C.F.R. 1.97(g) and (h), the filing of this IDS should not be construed as a representation that a search has been made or that information cited is, or is considered to be, material to patentability as defined in §1.56 (b), or that any cited document listed or attached is (or constitutes) prior art. Unless other-wise indicated, the date of publication indicated for an item is taken from the face of' the item and Applicant reserves the right to prove that the date of publication is in fact different.

Early and favorable consideration is earnestly solicited.

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

Dated: April 29, 2014

Respectfully submitted,

/kharihar/
Katherine Harihar, Reg. No. 71140, for
Clark G. Sullivan
Registration No. 36942
Troutman Sanders LLP
The Chrysler Building
405 Lexington Avenue
New York, New York 10174
Direct Tel: (212) 704-6105
Fax: (212) 704-6288
Direct E-mail:
clark.sullivan@troutmansanders.com
Attorneys/Agents for Applicant

UNITED STATES PATENT AND TRADEMARK OFFICE

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www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
14/069,927	11/01/2013	Fabio TRENTO	244168.000015US4

CONFIRMATION NO. 3207

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

PUBLICATION NOTICE

OC000000069513982

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

Publication No.US-2014-0194395-A1
Publication Date:07/10/2014

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

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	14069927
Filing Date	2013-11-01
First Named Inventor	Fabio TRENTO
Art Unit	1612
Examiner Name	Walter E. WEBB
Attorney Docket Number	244168.000015US4

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14069927
	Filing Date	2013-11-01
	First Named Inventor	Fabio TRENTO
	Art Unit	1612
	Examiner Name	Walter E. WEBB
	Attorney Docket Number	244168.000015US4

	1	European Search Report dated April 3, 2014, from corresponding European Application Number 14151676.5.	☐
	2	European Search Report dated March 25, 2014, from corresponding European Application Number 14151678.1.	☐
	3	European Search Report dated April 3, 2014, from corresponding European Application Number 14151683.1.	☐

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EXAMINER SIGNATURE

Examiner Signature		Date Considered	

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

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

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	14069927
	Filing Date	2013-11-01
	First Named Inventor	Fabio TRENTO
	Art Unit	1612
	Examiner Name	Walter E. WEBB
	Attorney Docket Number	244168.000015US4

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).

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☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

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

Signature	/Clark G. Sullivan/	Date (YYYY-MM-DD)	2014-09-11
Name/Print	Clark G. Sullivan	Registration Number	36,942

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

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

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

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(19) World Intellectual Property Organization
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(10) International Publication Number
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60/887,840 2 February 2007 (02.02.2007) US

(71) Applicant *(for all designated States except US)*: **PFIZER LIMITED** [GB/GB]; Ramsgate Road, Sandwich, Kent CT13 9NJ (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **ANDREWS, Mark, David** [GB/GB]; Pfizer Global Research and Development, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB). **BROWN, Alan, Daniel** [GB/GB]; Pfizer Global Research and Development, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB). **LANSDELL, Mark, Ian** [GB/GB]; Pfizer Global Research and Development, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB). **SUMMERHILL, Nicholas, William** [GB/GB]; Pfizer Global Research and Development, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB).

(74) Agent: **DROUIN, Stéphane**; Pfizer Global Research and Development, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB).

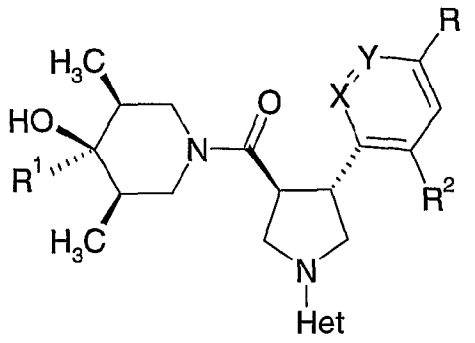
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(54) Title: MELANOCORTIN TYPE 4 RECEPTOR AGONIST PIPERIDINOYLPYRROLIDINES



(I)

(57) Abstract: The present invention relates to a class of melanocortin MCR4 agonists of general formula (I), wherein the variables and substituents are as defined herein and especially to selective MCR4 agonist compounds, to their use in medicine, particularly in the treatment of sexual dysfunction and obesity, to intermediates useful in their synthesis and to compositions containing them.

WO 2007/096763 A2

MELANOCORTIN TYPE 4 RECEPTOR AGONIST PIPERIDINOYLPYRROLIDINES

This present invention relates to a certain class of compounds, and their pharmaceutically acceptable salts, solvates and prodrugs thereof, which are agonists at the melanocortin 4 (MC4) receptor, especially to selective MC4 agonist compounds, to their use in medicine, to compositions containing them, to processes for their preparation and to intermediates used in such processes. In particular the present invention relates to a class of MCR4 agonist piperidinoylpyrrolidine compounds useful for the treatment of sexual dysfunctions, obesity, diabetes and other disorders. [The terms "MC4", "MC4 receptor", "MCR4", "MC4-R", etc. are used interchangeably herein.]

Melanocortins are peptides derived from pro-opiomelanocortins (POMC) that bind to and activate G-protein coupled receptors (GPCR's) of the melanocortin receptor family. Melanocortins regulate a diverse number of physiological processes including sexual function and sexual behaviour, food intake and metabolism. There are five melanocortin receptors that have been cloned, MCR1, MCR2, MCR3, MCR4, MCR5, and are expressed in various tissues. MCR1 is specifically expressed in melanocytes and melanoma cells, MCR2 is the ACTH receptor and is expressed in adrenal tissue, MCR3 is predominantly expressed in the brain and limbic system, MCR4 is widely expressed in the brain and spinal cord, and MCR5 is expressed in the brain and many peripheral tissues including skin, adipose tissue, skeletal muscle, and lymphoid tissue. MCR3 may be involved in the control of sexual function, food intake and thermogenesis.

MC4-R is a G-protein–coupled seven-transmembrane receptor primarily expressed in the hypothalamus, hippocampus, and thalamus (Gantz et al. 1993 *J Biol Chem* 268:15174–15179). The receptor is implicated in the central regulation of body weight: MC4-R is activated by α-melanocyte-stimulating hormone (MSH), which is derived from pro-opiomelanocortin and is inactivated by agouti gene-related protein (AGRP). α-MSH induces weight loss, whereas the ectopic expression of agouti protein results in obesity in the agouti mice (Fan et al. 1993 *Nature* 385:165–168; Lu et al. 1994 *Nature* 371:799–802). Additional evidence for the role of MC4-R in weight regulation stems from both a knockout model in mice (Huszar et al. 1997 *Cell* 88:131–141) and haploinsufficiency mutations in humans (Vaisse et al. 1998 *Nat Genet* 20:113–114; Yeo et al. 1998 *Nat Genet* 20:111–112; Hinney et al. 1999 *J Clin Endocrinol Metab* 84:1483–1486). In *MC4-R*–knockout mice, an increased body weight was discernible by age 5 wk. By age 15 wk, homozygous mutant females were, on average, twice as heavy as their wild-type littermates, whereas homozygous mutant males were ~50% heavier than wild-type controls. Mice heterozygous for the *MC4-R* knockout showed a weight gain intermediate to that seen in wild-type and homozygous mutant littermates, thus demonstrating a gene dosage effect of MC4-R ablation on body-weight regulation. The food intake of homozygous mutants was increased by ~50% in comparison to that in wild-type sibs (Huszar et al. 1997 *Cell* 88:131–141). [From *Am. J. Hum. Genet.*, 65:1501-1507,1999]. MCR4 activation has been shown to induce penile erection in rodents and MCR4 inactivation has been shown to cause obesity (reviewed in Hadley, 1999, Ann N Y Acad Sci., 885:1-21, Wikberg et al 2000, Pharmacol Res., 42(5), 393-420).

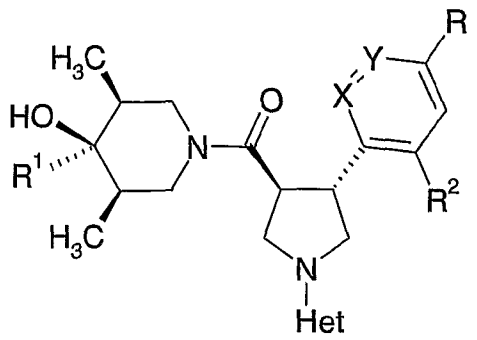
Chaki and Nakazato, in Drugs Of The Future, 2004, 29(10): 1065-1074, refer to potential therapeutic applications for ligands acting at the MC4 receptor. International Patent Application publication numbers WO 2005/077935, WO 02/068387 and WO 02/068388, and International Patent Application PCT/IB2006/002151 refer to certain piperidinylcarbonylpyrrolidines as MC4 agonists useful in treating sexual dysfunctions, obesity, diabetes and other disorders. The preceding publications are hereby incorporated by reference in their entirety, with regard to the therapeutic aspects of the MC4 agonists of this invention.

Compounds of the present invention are useful in treating diseases, disorders or conditions responsive to activation of the MC4 receptor, including :
male and female sexual dysfunctions including hypoactive sexual desire disorder, sexual arousal disorder, orgasmic disorder and/or sexual pain disorder in females, male erectile dysfunction;
obesity (by reducing appetite, increasing metabolic rate, reducing fat intake or reducing carbohydrate craving); and
diabetes mellitus (by enhancing glucose tolerance and/or decreasing insulin resistance).
The compounds of the invention are potentially useful in treating further diseases, disorders or conditions including, but not limited to, hypertension, hyperlipidemia, osteoarthritis, cancer, gall bladder disease, sleep apnea, depression, anxiety, compulsion, neuroses, insomnia/sleep disorder, substance abuse, pain, fever, inflammation, immune modulation, rheumatoid arthritis, skin tanning, acne and other skin disorders, neuroprotective and cognitive and memory enhancement including the treatment of Alzheimer's disease, treatment of Lower Urinary Tract Dysfunction (including Urinary Incontinence - overactive bladder, increased daytime frequency, nocturia, urgency, urinary incontinence (any condition in which there is an involuntary leakage of urine), including stress urinary incontinence, urge urinary incontinence and mixed urinary incontinence, overactive bladder with associated urinary incontinence, enuresis, nocturnal enuresis, continuous urinary incontinence, situational urinary incontinence such as incontinence during sexual intercourse, and lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH)), and any other indications mentioned in the above-referenced patent applications..
Compounds of the present invention are particularly suitable for treating female sexual dysfunction, male erectile dysfunction, obesity, diabetes, and conditions of Lower Urinary Tract Dysfunction.

The terms "treating", "treat", or "treatment" as used herein are intended to embrace both prevention and control i.e., prophylactic, and palliative treatment of the indicated conditions.

Desirable properties for MCR4 agonist compounds of the present invention include: desirable MCR4 agonist potencies as detailed hereinafter; selectivity for MCR4 agonism versus MCR1, and/or MCR5, and/or MCR3 as detailed hereinafter; both desirable MC4R agonist potency and selectivity for MCR4 versus, MCR1, and/or MCR5, and/or MCR3; good biopharmaceutical properties such as physical stability; solubility; oral bioavailability; appropriate metabolic stability; ability to displace AGRP from the MC4 receptor.

The present invention provides for compounds of formula (I):



(I)

wherein

one of X and Y is N and the other is CH,

R is F, Cl, CN, CF_3 or methoxy, with the proviso that when Y is N, R is not F or Cl,

R^1 is phenyl, 2-pyridyl, C_3-C_6 cycloalkyl or CH_2(C_3-C_6 cycloalkyl), wherein the ring moiety is optionally substituted by one or more substituents independently selected from F, Cl, CN, methyl and methoxy,

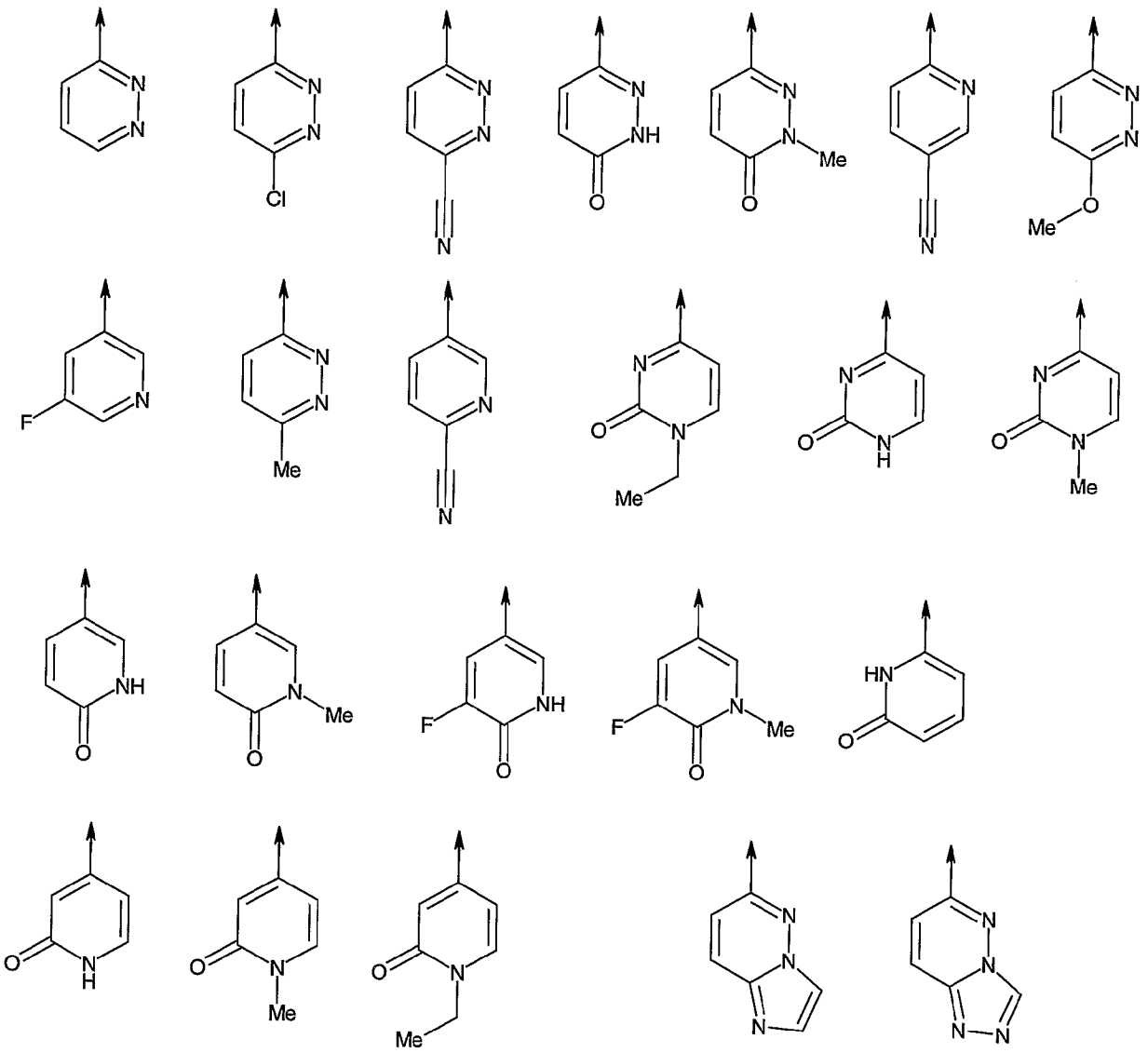
R^2 is H, F or Cl, with the proviso that when Y is N, R^2 is not F or Cl,

Het is a 6-membered ring containing one or 2 N atoms, wherein the ring is either aromatic, or contains 2 double bonds in the ring and a =O substituent, which ring is optionally substituted by one or more substituents independently selected from F, Cl, OH, CN, methyl, ethyl, NH_2, $NHCH_3$, $N(CH_3)_2$ and methoxy,

or alternatively, Het is a 6-membered ring containing one or 2 N atoms fused at the 3,4-positions, relative to the attachment to the pyrrolidine ring, to a 5-membered aromatic ring containing one or two further N atoms, which 5-membered ring is optionally substituted by OH.

and the pharmaceutically acceptable salts, solvates (including hydrates), and prodrugs thereof.

Non-limiting examples of suitable "Het" groups are shown below:



Preferably X is N and Y is CH.

Preferably R is chloro.

Preferably R^1 is phenyl optionally substituted by one or more substituents independently selected from F, Cl, CN, methyl and methoxy.

More preferably R^1 is phenyl, 4-chlorophenyl or 4-fluorophenyl.

In an alternative embodiment R^1 is preferably C_3-C_6 cycloalkyl, more preferably cyclopropyl or cyclohexyl.

Preferably R^2 is H or F.

More preferably R^2 is H.

Preferably Het is pyridin-2-yl, pyridin-3-yl, pyridazin-3-yl, 6-oxo-1,6-dihydropyridazin-3-yl, 6-oxo-1,6-dihydropyridin-3-yl, 2-oxo-1,2-dihydropyrimidin-4-yl, 6-oxo-1,6-dihydropyrimidin-4-yl, 2-oxo-1,2-dihydropyridin-4-yl, imidazo[1,2-b]pyridazin-6-yl, [1,2,4]triazolo[4,3-b]pyridazin-6-yl or 6-oxo-1,6-dihydropyridin-2-yl, optionally substituted by one or more substituents independently selected from F, Cl, OH, CN, methyl, ethyl and methoxy.

More preferably Het is pyridin-2-yl, pyridin-3-yl, pyridazin-3-yl or 6-oxo-1,6-dihydropyridazin-3-yl, optionally substituted by one or more substituents independently selected from OH, CN, F, methyl and methoxy.

Yet more preferably Het is pyridin-2-yl or pyridazin-3-yl, each of which is substituted at the para-position relative to the bond linking to the pyrrolidine moiety, by OH, CN or methoxy.

Most preferably Het is pyridazin-3-yl substituted at the para-position relative to the bond linking to the pyrrolidine moiety, by OH, CN or methoxy.

A preferred group of compounds, salts, solvates and prodrugs include those wherein :
R^1 has the value associated with the following specific compounds.

A preferred group of compounds, salts, solvates and prodrugs include those wherein :
R has the value associated with the following specific compounds.

A preferred group of compounds, salts, solvates and prodrugs include those wherein :
R^2 has the value associated with the following specific compounds.

A preferred group of compounds, salts, solvates and prodrugs include those wherein :
Het has the value associated with the following specific compounds.

A further preferred group of compounds, salts, solvates and prodrugs include those wherein :
R, R^1, R^2 and Het have the values associated with the following specific compounds.

Preferably the compound is selected from:

6-[(3S,4S)-3-(5-chloropyridin-2-yl)-4-{[(3R,4R,5S)-4-(4-fluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]pyridazine-3-carbonitrile;

6-[(3S,4S)-3-(5-chloropyridin-2-yl)-4-{[(3R,4R,5S)-4-hydroxy-3,5-dimethyl-4-phenylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]pyridazine-3-carbonitrile;

6-[(3S,4S)-3-(5-chloropyridin-2-yl)-4-{[(3R,4R,5S)-4-hydroxy-3,5-dimethyl-4-pyridin-2-ylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]pyridazine-3-carbonitrile;

6-[(3S,4S)-3-(5-chloropyridin-2-yl)-4-{[(3R,4R,5S)-4-hydroxy-3,5-dimethyl-4-phenylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]pyridazin-3(2H)-one;

6-[(3S,4S)-3-(5-chloropyridin-2-yl)-4-{[(3R,4R,5S)-4-hydroxy-3,5-dimethyl-4-phenylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]-2-methylpyridazin-3(2H)-one;

6-[(3S,4S)-3-{[(3R,4R,5S)-4-(4-chlorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}-4-(5-chloropyridin-2-yl)pyrrolidin-1-yl]-2-methylpyridazin-3(2H)-one;

6-[(3S,4S)-3-(5-chloropyridin-2-yl)-4-{[(3R,4R,5S)-4-(5-chloropyridin-2-yl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]-2-methylpyridazin-3(2H)-one;

6-[(3S,4S)-3-(5-chloropyridin-2-yl)-4-{[(3R,4R,5S)-4-(3,4-difluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]-2-methylpyridazin-3(2H)-one;

6-[(3S,4S)-3-(5-chloropyridin-2-yl)-4-{[(3R,4R,5S)-4-hydroxy-4-(4-methoxyphenyl)-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]-2-methylpyridazin-3(2H)-one;

6-[(3S,4S)-3-(5-chloropyridin-2-yl)-4-{[(3R,4R,5S)-4-cyclohexyl-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]-2-methylpyridazin-3(2H)-one;

(3R,4R,5S)-1-{[(3S,4S)-1-(6-chloropyridazin-3-yl)-4-(5-chloropyridin-2-yl)pyrrolidin-3-yl]carbonyl}-4-(4-fluorophenyl)-3,5-dimethylpiperidin-4-ol;

(3R,4R,5S)-1-{[(3S,4S)-4-(5-chloropyridin-2-yl)-1-(6-methoxypyridazin-3-yl)pyrrolidin-3-yl]carbonyl}-4-cyclopropyl-3,5-dimethylpiperidin-4-ol;

(3R,4R,5S)-1-{[(3S,4S)-4-(5-chloropyridin-2-yl)-1-(5-fluoropyridin-3-yl)pyrrolidin-3-yl]carbonyl}-4-(4-fluorophenyl)-3,5-dimethylpiperidin-4-ol;

6-[(3S,4S)-3-(5-chloropyridin-2-yl)-4-{[(3R,4R,5S)-4-(4-fluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]nicotinonitrile;

6-[(3S,4S)-3-{[(3R,4R,5S)-4-(4-fluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}-4-(5-fluoropyridin-2-yl)pyrrolidin-1-yl]pyridazine-3-carbonitrile;

6-[(3S,4S)-3-(5-fluoropyridin-2-yl)-4-{[(3R,4R,5S)-4-hydroxy-3,5-dimethyl-4-phenylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]pyridazine-3-carbonitrile;

6-[(3S,4S)-3-{[(3R,4R,5S)-4-(4-chlorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}-4-(5-fluoropyridin-2-yl)pyrrolidin-1-yl]pyridazine-3-carbonitrile;

6-[(3S,4S)-3-{[(3R,4R,5S)-4-(4-chlorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}-4-(5-fluoropyridin-2-yl)pyrrolidin-1-yl]pyridazin-3(2H)-one;

6-[(3S,4S)-3-(5-cyanopyridin-2-yl)-4-{[(3R,4R,5S)-4-(4-fluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]pyridazine-3-carbonitrile;

6-[(3S,4R)-3-{[(3R,4R,5S)-4-(4-fluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}-4-(6-methoxypyridin-3-yl)pyrrolidin-1-yl]pyridazine-3-carbonitrile;

6-[(3S,4S)-3-{[(3R,4R,5S)-4-(4-fluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}-4-(5-methoxypyridin-2-yl)pyrrolidin-1-yl]pyridazine-3-carbonitrile;

(3R,4R,5S)-4-(4-fluorophenyl)-1-{[(3S,4R)-1-(5-fluoropyridin-3-yl)-4-(6-methoxypyridin-3-yl)pyrrolidin-3-yl]carbonyl}-3,5-dimethylpiperidin-4-ol;

(3R,4R,5S)-1-{[(3S,4S)-4-(5-chloropyridin-2-yl)-1-pyridazin-3-ylpyrrolidin-3-yl]carbonyl}-4-(4-fluorophenyl)-3,5-dimethylpiperidin-4-ol;

6-[(3S,4S)-3-(5-chloropyridin-2-yl)-4-{[(3R,4R,5S)-4-(4-fluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]pyridazin-3(2H)-one;

6-[(3S,4S)-3-(5-chloropyridin-2-yl)-4-{[(3R,4R,5S)-4-(4-fluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]-2-methylpyridazin-3(2H)-one;

(3R,4R,5S)-1-{[(3S,4S)-4-(5-chloropyridin-2-yl)-1-[1,2,4]triazolo[4,3-b]pyridazin-6-ylpyrrolidin-3-yl]carbonyl}-4-(4-fluorophenyl)-3,5-dimethylpiperidin-4-ol;

(3R,4R,5S)-1-{[(3S,4S)-4-(5-chloropyridin-2-yl)-1-imidazo[1,2-b]pyridazin-6-ylpyrrolidin-3-yl]carbonyl}-4-(4-fluorophenyl)-3,5-dimethylpiperidin-4-ol;

4-[(3S,4S)-3-(5-chloropyridin-2-yl)-4-{[(3R,4R,5S)-4-(4-fluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]pyrimidin-2(1H)-one;

4-[(3S,4S)-3-(5-chloropyridin-2-yl)-4-{[(3R,4R,5S)-4-(4-fluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]-1-methylpyrimidin-2(1H)-one;

(3R,4R,5S)-1-{[(3S,4S)-4-(5-chloropyridin-2-yl)-1-(6-methoxypyridazin-3-yl)pyrrolidin-3-yl]carbonyl}-4-(4-fluorophenyl)-3,5-dimethylpiperidin-4-ol;

6-[(3S,4S)-3-(5-chloro-3-fluoropyridin-2-yl)-4-{[(3R,4R,5S)-4-(4-fluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]pyridazine-3-carbonitrile;

6-[(3S,4S)-3-(5-chloro-3-fluoropyridin-2-yl)-4-{[(3R,4R,5S)-4-(4-fluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]pyridazin-3(2H)-one;

6-[(3S,4S)-3-(5-chloro-3-fluoropyridin-2-yl)-4-{[(3R,4R,5S)-4-(4-fluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]-2-methylpyridazin-3(2H)-one;

6-[(3S,4S)-3-(3,5-difluoropyridin-2-yl)-4-{[(3R,4R,5S)-4-(4-fluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]pyridazine-3-carbonitrile;

6-[(3S,4S)-3-(3,5-difluoropyridin-2-yl)-4-{[(3R,4R,5S)-4-(4-fluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]pyridazin-3(2H)-one;

6-[(3S,4S)-3-(3,5-difluoropyridin-2-yl)-4-{[(3R,4R,5S)-4-(4-fluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]-2-methylpyridazin-3(2H)-one;

6-[(3S,4S)-3-{[(3R,4R,5S)-4-(4-chlorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}-4-(5-chloropyridin-2-yl)pyrrolidin-1-yl]pyridazine-3-carbonitrile;

6-[(3S,4S)-3-(5-chloropyridin-2-yl)-4-{[(3R,4R,5S)-4-(3,4-difluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]pyridazine-3-carbonitrile;

6-[(3S,4S)-3-{[(3R,4R,5S)-4-(4-chlorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}-4-(5-chloropyridin-2-yl)pyrrolidin-1-yl]pyridazin-3(2H)-one;

6-[(3S,4S)-3-(5-chloropyridin-2-yl)-4-{[(3R,4R,5S)-4-(3,4-difluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]pyridazin-3(2H)-one;

and the pharmaceutically acceptable salts, solvates (including hydrates), and prodrugs thereof.

More preferably the compound is selected from:

6-[(3S,4S)-3-(5-chloropyridin-2-yl)-4-{[(3R,4R,5S)-4-(4-fluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]pyridazine-3-carbonitrile;

6-[(3S,4S)-3-(5-chloropyridin-2-yl)-4-{[(3R,4R,5S)-4-hydroxy-3,5-dimethyl-4-phenylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]pyridazine-3-carbonitrile;

6-[(3S,4S)-3-(5-chloropyridin-2-yl)-4-{[(3R,4R,5S)-4-hydroxy-3,5-dimethyl-4-phenylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]pyridazin-3(2H)-one;

6-[(3S,4S)-3-(5-chloropyridin-2-yl)-4-{[(3R,4R,5S)-4-hydroxy-3,5-dimethyl-4-phenylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]-2-methylpyridazin-3(2H)-one;

6-[(3S,4S)-3-{[(3R,4R,5S)-4-(4-chlorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}-4-(5-chloropyridin-2-yl)pyrrolidin-1-yl]-2-methylpyridazin-3(2H)-one;

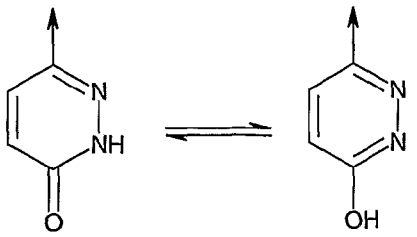
6-[(3S,4S)-3-(5-chloropyridin-2-yl)-4-{[(3R,4R,5S)-4-(5-chloropyridin-2-yl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]-2-methylpyridazin-3(2H)-one;
6-[(3S,4S)-3-(5-chloropyridin-2-yl)-4-{[(3R,4R,5S)-4-(3,4-difluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]-2-methylpyridazin-3(2H)-one;
(3R,4R,5S)-1-{[(3S,4S)-4-(5-chloropyridin-2-yl)-1-pyridazin-3-ylpyrrolidin-3-yl]carbonyl}-4-(4-fluorophenyl)-3,5-dimethylpiperidin-4-ol;
6-[(3S,4S)-3-(5-chloropyridin-2-yl)-4-{[(3R,4R,5S)-4-(4-fluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]pyridazin-3(2H)-one;
6-[(3S,4S)-3-(5-chloropyridin-2-yl)-4-{[(3R,4R,5S)-4-(4-fluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]-2-methylpyridazin-3(2H)-one;
(3R,4R,5S)-1-{[(3S,4S)-4-(5-chloropyridin-2-yl)-1-[1,2,4]triazolo[4,3-b]pyridazin-6-ylpyrrolidin-3-yl]carbonyl}-4-(4-fluorophenyl)-3,5-dimethylpiperidin-4-ol;
(3R,4R,5S)-1-{[(3S,4S)-4-(5-chloropyridin-2-yl)-1-imidazo[1,2-b]pyridazin-6-ylpyrrolidin-3-yl]carbonyl}-4-(4-fluorophenyl)-3,5-dimethylpiperidin-4-ol;
4-[(3S,4S)-3-(5-chloropyridin-2-yl)-4-{[(3R,4R,5S)-4-(4-fluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]pyrimidin-2(1H)-one;
4-[(3S,4S)-3-(5-chloropyridin-2-yl)-4-{[(3R,4R,5S)-4-(4-fluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]-1-methylpyrimidin-2(1H)-one;
6-[(3S,4S)-3-(5-chloro-3-fluoropyridin-2-yl)-4-{[(3R,4R,5S)-4-(4-fluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]pyridazine-3-carbonitrile;
6-[(3S,4S)-3-(5-chloro-3-fluoropyridin-2-yl)-4-{[(3R,4R,5S)-4-(4-fluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]pyridazin-3(2H)-one;
6-[(3S,4S)-3-(5-chloro-3-fluoropyridin-2-yl)-4-{[(3R,4R,5S)-4-(4-fluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]-2-methylpyridazin-3(2H)-one;
6-[(3S,4S)-3-(3,5-difluoropyridin-2-yl)-4-{[(3R,4R,5S)-4-(4-fluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]pyridazine-3-carbonitrile;
6-[(3S,4S)-3-(3,5-difluoropyridin-2-yl)-4-{[(3R,4R,5S)-4-(4-fluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]pyridazin-3(2H)-one;
6-[(3S,4S)-3-(3,5-difluoropyridin-2-yl)-4-{[(3R,4R,5S)-4-(4-fluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]-2-methylpyridazin-3(2H)-one;
6-[(3S,4S)-3-{[(3R,4R,5S)-4-(4-chlorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}-4-(5-chloropyridin-2-yl)pyrrolidin-1-yl]pyridazine-3-carbonitrile;
6-[(3S,4S)-3-(5-chloropyridin-2-yl)-4-{[(3R,4R,5S)-4-(3,4-difluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]pyridazine-3-carbonitrile;
6-[(3S,4S)-3-{[(3R,4R,5S)-4-(4-chlorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}-4-(5-chloropyridin-2-yl)pyrrolidin-1-yl]pyridazin-3(2H)-one;
6-[(3S,4S)-3-(5-chloropyridin-2-yl)-4-{[(3R,4R,5S)-4-(3,4-difluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]pyridazin-3(2H)-one;
and the pharmaceutically acceptable salts, solvates (including hydrates), and prodrugs thereof.

Most preferably the compound is selected from:

6-[(3S,4S)-3-(5-chloropyridin-2-yl)-4-{[(3R,4R,5S)-4-(4-fluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]pyridazine-3-carbonitrile;
6-[(3S,4S)-3-{[(3R,4R,5S)-4-(4-chlorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}-4-(5-chloropyridin-2-yl)pyrrolidin-1-yl]-2-methylpyridazin-3(2H)-one;
6-[(3S,4S)-3-(5-chloropyridin-2-yl)-4-{[(3R,4R,5S)-4-(5-chloropyridin-2-yl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]-2-methylpyridazin-3(2H)-one;
6-[(3S,4S)-3-(5-chloropyridin-2-yl)-4-{[(3R,4R,5S)-4-(3,4-difluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]-2-methylpyridazin-3(2H)-one;
6-[(3S,4S)-3-(5-chloropyridin-2-yl)-4-{[(3R,4R,5S)-4-(4-fluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]pyridazin-3(2H)-one;
6-[(3S,4S)-3-(5-chloropyridin-2-yl)-4-{[(3R,4R,5S)-4-(4-fluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]-2-methylpyridazin-3(2H)-one;
6-[(3S,4S)-3-{[(3R,4R,5S)-4-(4-chlorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}-4-(5-chloropyridin-2-yl)pyrrolidin-1-yl]pyridazine-3-carbonitrile;
6-[(3S,4S)-3-(5-chloropyridin-2-yl)-4-{[(3R,4R,5S)-4-(3,4-difluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]pyridazine-3-carbonitrile;
6-[(3S,4S)-3-{[(3R,4R,5S)-4-(4-chlorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}-4-(5-chloropyridin-2-yl)pyrrolidin-1-yl]pyridazin-3(2H)-one;
6-[(3S,4S)-3-(5-chloropyridin-2-yl)-4-{[(3R,4R,5S)-4-(3,4-difluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]pyridazin-3(2H)-one;
and the pharmaceutically acceptable salts, solvates (including hydrates), and prodrugs thereof.

The pharmaceutically acceptable salts of the compounds of the formula (I) include the acid addition salts thereof. Suitable acid addition salts are formed from acids which form non-toxic salts. Examples include the acetate, adipate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulphate/sulphate, borate, camsylate, citrate, cyclamate, edisylate, esylate, formate, fumarate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, isethionate, lactate, malate, maleate, malonate, mesylate, methylsulphate, naphthylate, 2-napsylate, nicotinate, nitrate, orotate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, pyroglutamate, saccharate, stearate, succinate, tannate, tartrate, tosylate, trifluoroacetate and xinofoate salts. Hemisalts of the acids may also be formed, for example, hemisulphate. For a review on suitable salts, see Handbook of Pharmaceutical Salts: Properties, Selection, and Use by Stahl and Wermuth (Wiley-VCH, 2002).

The compounds, salts, solvates and prodrugs of the invention may exist in tautomeric, zwitterionic, polymorphic, crystalline, liquid crystalline, etc. forms. All such forms are included within the scope of the invention. As an example to illustrate a tautomeric relationship, the compound where for example the "Het" group is as shown below, both "keto" and "enol" tautomers below are included within the scope of "Het" for the compounds of formula (I):



"keto" "enol"

Also included within the scope of the invention are multi-component complexes (other than salts and solvates) wherein the drug and at least one other component are present in stoichiometric or non-stoichiometric amounts. Complexes of this type include clathrates (drug-host inclusion complexes) and co-crystals. The latter are typically defined as crystalline complexes of neutral molecular constituents which are bound together through non-covalent interactions, but could also be a complex of a neutral molecule with a salt.

Also included within the scope of the invention are isotopically labelled compounds of formula (I), for example where ^{2}H, ^{3}H, ^{13}C, ^{15}N, ^{18}O or other isotopes, are incorporated, which may be made by suitable variation of the synthetic methods described herein using methods and reagents known in the art or routine modification thereof.

As indicated, so-called 'prodrugs' of the compounds of formula (I) are within the scope of the invention. Thus certain derivatives of compounds of formula (I), which may have little or no pharmacological activity themselves, can, when administered into or onto the body, be converted into compounds of formula (I) having the desired activity, for example, by hydrolytic cleavage. Such derivatives are referred to as 'prodrugs'. Further information on the use of prodrugs may be found in Pro-drugs as Novel Delivery Systems, Vol. 14, ACS Symposium Series (T Higuchi and W Stella) and Bioreversible Carriers in Drug Design, Pergamon Press, 1987 (Ed. E B Roche, American Pharmaceutical Association).

Certain compounds of formula (I) may also themselves act as prodrugs of other compounds of formula (I).

Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC).

Alternatively, the racemate (or a racemic precursor) may be reacted with a suitable optically active compound, for example, an alcohol, or, in the case where the compound of formula (I) contains an acidic or basic moiety, an acid or base such as tartaric acid or 1-phenylethylamine. The resulting diastereomeric mixture may be separated by chromatography and/or fractional crystallization and one or

both of the diastereoisomers converted to the corresponding pure enantiomer(s) by means well known to a skilled person.

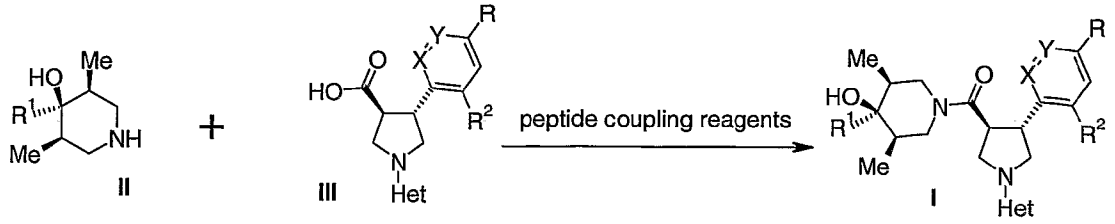
Chiral compounds of the invention (and chiral precursors thereof) may be obtained in enantiomerically-enriched form using chromatography, typically HPLC, on an asymmetric resin with a mobile phase consisting of a hydrocarbon, typically heptane or hexane, containing from 0 to 50% by volume of isopropanol, typically from 2 to 20%, and may contain from 0 to 5% by volume of an alkylamine. Concentration of the eluate affords the enriched mixture. The absolute composition of the mobile phase will be dependant upon the chiral stationary phase (asymmetric resin) selected.

The routes below, including those mentioned in the Examples and Preparations, illustrate methods of synthesising compounds of formula (I). The skilled person will appreciate that the compounds of the invention, and intermediates thereto, could be made by methods other than those specifically described herein, for example by adaptation of the methods described herein, for example by methods known in the art. Suitable guides to synthesis, functional group interconversions, use of protecting groups, etc., are for example:
"Comprehensive Organic Transformations" by RC Larock, VCH Publishers Inc. (1989); Advanced Organic Chemistry" by J. March, Wiley Interscience (1985); "Designing Organic Synthesis" by S Warren, Wiley Interscience (1978); "Organic Synthesis – The Disconnection Approach" by S Warren, Wiley Inetrscience (1982); "Guidebook to Organic Synthesis" by RK Mackie and DM Smith, Longman (1982); "Protective Groups in Organic Synthesis" by TW Greene and PGM Wuts, John Wiley and Sons, Inc. (1999); and "Protecting Groups" by PJ, Kocienski, Georg Thieme Verlag (1994); and any updated versions of said standard works.

In the general synthetic methods below, unless otherwise specified, the substituents R, R^1, R^2, X, Y and Het are as defined above with reference to the compounds of formula (I) above.

The routes below illustrate methods of synthesising compounds of formula (I). The skilled person will appreciate that other methods may be equally as viable.

Scheme 1 illustrates the preparation of compounds of formula (I) via peptide coupling of intermediates (II) and (III), if necessary adding a suitable base and/or additive (such as 1-hydroxybenzotriazole hydrate or 4-dimethylaminopyridine).

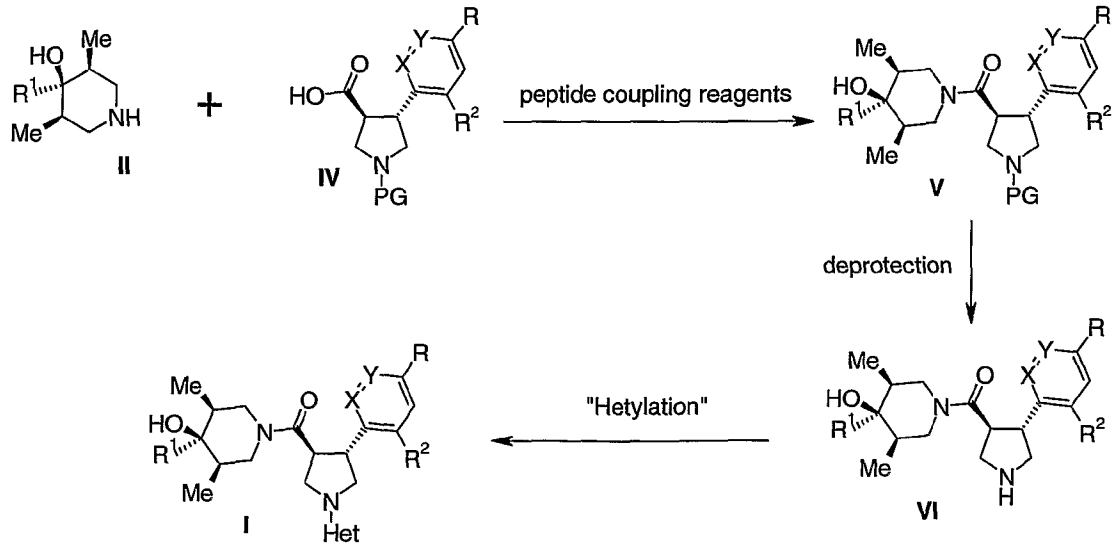


Scheme 1

Alternative conditions employed involve stirring a solution of the piperidine of general formula (II) and the acid of general formula (III) together with 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (EDCI), triethylamine or *N*-methylmorpholine and 1-hydroxybenzotriazole hydrate (HOBt) in dimethylformamide (DMF), tetrahydrofuran (THF), dichloromethane (DCM) or ethyl acetate (EtOAc) at room temperature. A further alternative suitable procedure is to stir a solution of the intermediate compounds of general formula (II) and general formula (III) together with *O*-benzotriazol-1-yl-*N*,*N*,*N*',*N*'–tetramethyluronium hexafluorophosphate (HBTU) or 1-propylphosphonic acid cyclic anhydride in CH_2Cl_2 or EtOAc. Any suitable inert solvent may be used in place of those mentioned above, wherein inert solvent means a solvent which does not contain a carboxylic acid or primary or secondary amine. At least one equivalent of each of the coupling reagents should be used and an excess of either one or both may be used if desired.

According to a further embodiment the present invention provides novel intermediate compounds of general formula (III).

Scheme 2 illustrates an alternative route for the preparation of compounds of general formula (I), having a range of Het groups, *via* utility of a protecting group strategy.



Scheme 2

PG is a suitable nitrogen-protecting group.

Novel compounds of formulae (IV), (V) and (VI) are further embodiments of the invention.

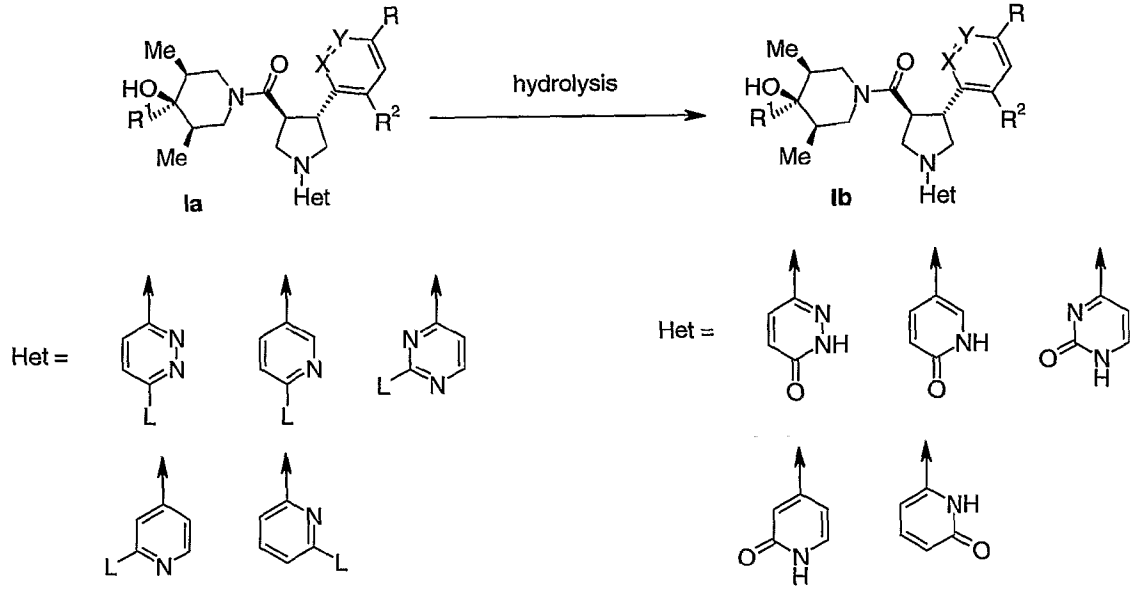
In scheme 2 the amine intermediates of general formula (II) and protected pyrrolidine acid intermediates of general formula (IV) are coupled using standard peptide coupling methods as previously described in scheme 1 to provide a coupled and protected intermediate of general formula (V) from which the nitrogen

protecting group can be removed using standard de-protection strategies to furnish a compound of general formula (VI). Any suitable nitrogen protecting groups may be used (as described in "Protecting Groups in Organic Synthesis" 3rd Edition T. W. Greene and P.G. Wuts, Wiley-Interscience, 1999). Common nitrogen protecting groups (PG) suitable for use herein include *tert*-butoxycarbonyl (t-Boc), which is readily removed by treatment with an acid such as trifluoroacetic acid or hydrogen chloride in an organic solvent such as dichloromethane or 1,4-dioxane, and benzyl, which is readily removed by hydrogenation in the presence of a suitable catalyst or by treatment with 1-chloroethyl chloroformate.

The "Het" group (where "Het" is a heteroaryl group) may be introduced by displacement of a suitable leaving group, for example from a heteroaromatic precursor of formula "Het-L" where L is a suitable leaving group. Suitable leaving groups include halogens. In certain cases transition metal catalysis (e.g. palladium, copper), optionally in combination with a phosphine ligand such as 1,1'-binaphthalene-2,2'-diylbisdiphenylphosphine, may be required to achieve the required coupling products.

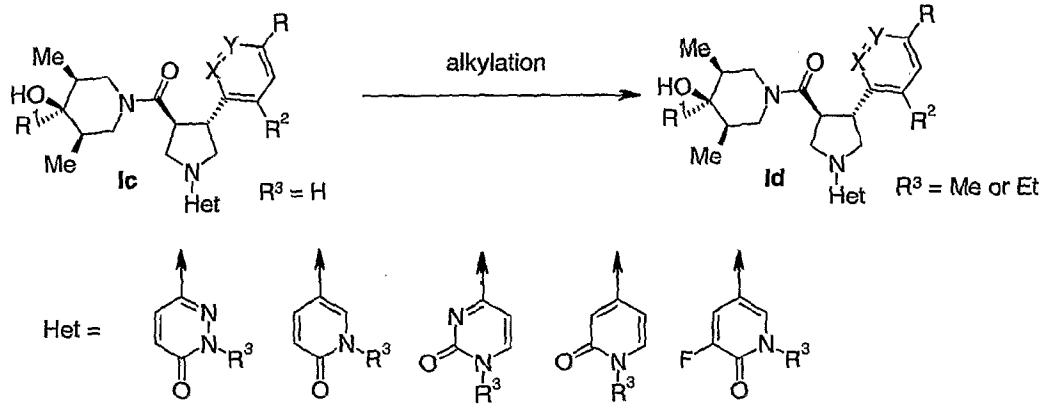
Alternatively, compounds of general formula (I) having particular Het groups may be converted into other compounds of general formula (I) having different Het groups. For example:

i) Compounds of formula (Ia) , where Het contains a suitable leaving group L, such as methoxy or chlorine, as shown in scheme 3, can be converted into compounds of formula (Ib), as shown in scheme 3, by hydrolysis under either acidic or basic conditions. Acidic conditions are preferred, and particularly preferred is treatment of compounds of formula (Ia) with acetic acid at reflux temperature. Alternatively, a compound of formula (Ia), where L is chloro, can be reacted with an alkoxide of formula $Z\text{-}O^-$, where Z is a suitable oxygen protecting group, to give an intermediate of formula (Ia), where L is OZ. Subsequent deprotection then provides the compounds of formula (Ib). For example, when Z = benzyl, it can readily be removed by hydrogenation in the presence of a suitable catalyst



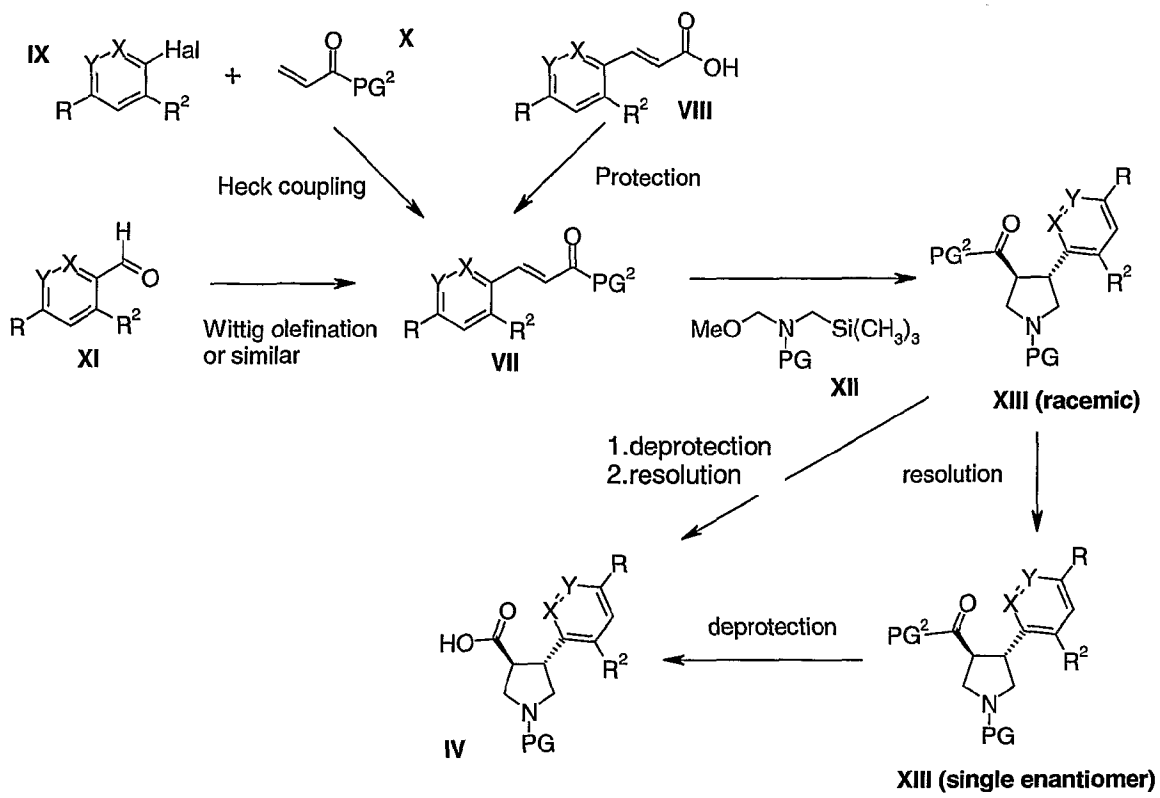
Scheme 3

ii) Compounds of formula Ic , where Het is as shown in scheme 4 and R^3 is H, can be converted into compounds of formula Id, where R^3 is methyl or ethyl, as shown in scheme 4, by treatment with a base and an alkylating agent in an appropriate solvent. Suitable bases include sodium hydride, lithium diisopropylamide and sodium hexamethyldisilazide, suitable alkylating agents include methyl iodide, methyl tosylate, dimethyl sulfate and ethyl iodide and suitable solvents include tetrahydrofuran, dimethylformamide and N-methyl-2-pyrrolidinone. An optional additive, such as a lithium salt, lithium bromide for example, may also be present in the reaction mixture.



Scheme 4

Scheme 5 illustrates the route for preparation of the pyrrolidine acid intermediates of general formula (IV) from unsaturated intermediates of general formula (VII).



Scheme 5

PG is a suitable nitrogen protecting group. PG^2 is a suitable carboxylic acid protecting group. Compounds of formulae (VIII), (IX), (X), (XI) and (XII) are either commercially available or will be well-known to those skilled in the art with reference to literature precedents and/or the preparations herein.

Compounds of general formula (VII) can be made predominantly as the desired *trans*-isomer by Wittig or similar olefination of an aldehyde intermediate of general formula (XI) with a suitable ylid e.g. methyl (triphenylphosphoranylidene)acetate, or a phosphonate anion e.g. derived from deprotonation of trimethylphosphonoacetate.

Many alternative methods exists in the literature for the production of unsaturated intermediates of general formula (VII), including protection of a precursor cinnamic acid derivative (VIII) using standard methods, or Heck reaction of an aromatic halide (IX) with a suitable acrylate derivative (X), such as *t*-butyl acrylate, in the presence of a palladium catalyst and a suitable base, such as triethylamine.

The resulting *E*-olefin intermediate of general formula (VII) will undergo a [3+2]-azomethine ylid cycloaddition by reaction with an ylid precursor of general formula (XII), to provide a pyrrolidine with almost exclusively the *trans*-stereochemistry. This reaction requires an inert solvent such as dichloromethane or toluene or tetrahydrofuran and activation by one or more of: (1) an acid catalyst, such as TFA; (2) a desilylating agent such as silver fluoride; (3) heating.

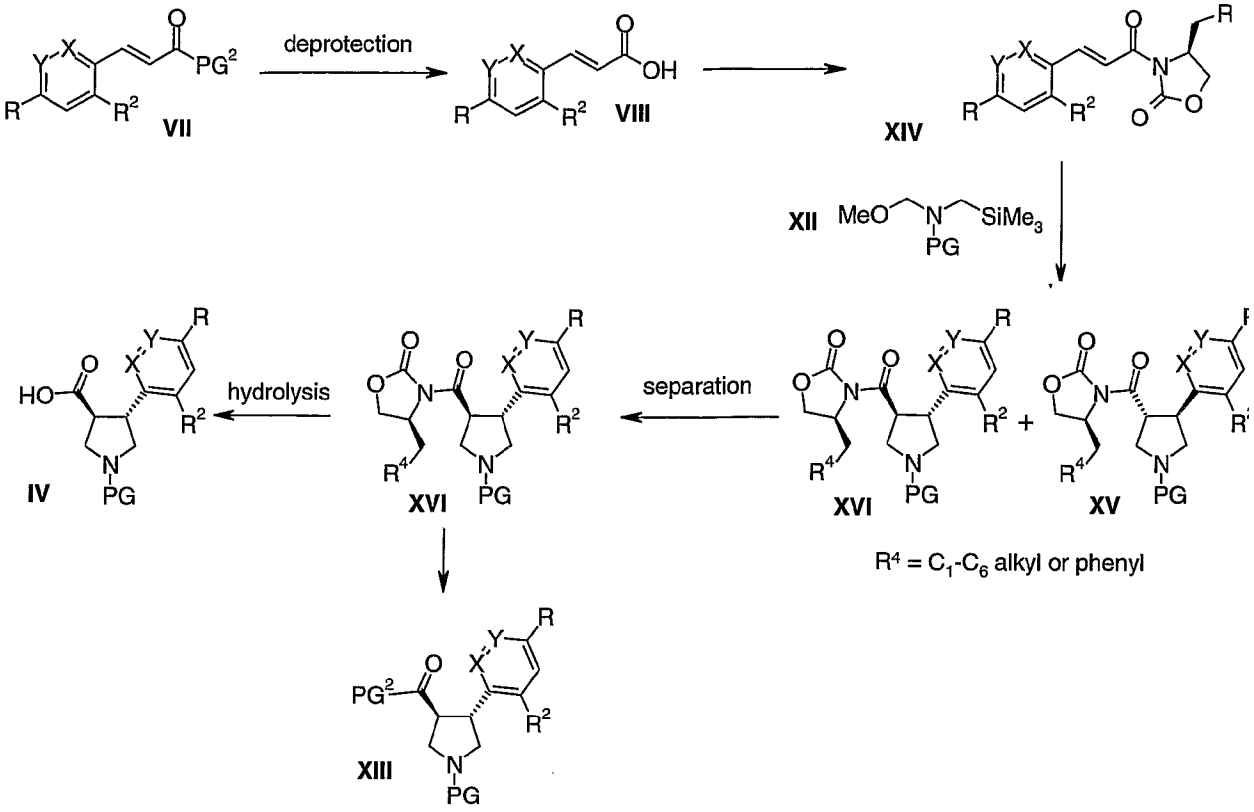
The compound of general formula (XIII) obtained from the cycloaddition reaction is a racemate and may require resolution into its constituent enantiomers, which can be achieved by preparative HPLC using a chiral stationary phase. Alternatively the acid intermediate of general formula (IV) can be resolved by standard methods (e.g. formation of diastereomeric derivatives by reaction with an enantiomerically pure reagent, separation of the resulting diastereomers by physical methods and cleaving to acid (IV).

Intermediate compounds of general formula (XIII) can be converted into compounds of general formula (IV) by deprotection of the protecting group PG^2. Many methods are available to achieve this transformation (see Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Fourth Edition. March, Jerry, 1992, pp 378-383 published by Wiley, New York, N. Y. USA). In particular, for base labile protecting groups, treatment of a compound of general formula (XIII) with an aqueous alkali metal hydroxide solution, such as lithium hydroxide, sodium hydroxide or potassium hydroxide in a suitable organic solvent will provide the corresponding compounds of general formula (IV). Preferably water-miscible organic co-solvents (such as 1,4-dioxane or tetrahydrofuran) are also utilised in such reactions. If required, the reaction may be heated to assist the hydrolysis. Certain protecting groups are more conveniently hydrolysed in acidic conditions e.g. *tert*-butyl or benzhydryl esters. Such esters can be cleaved by treatment with anhydrous acids such as trifluoroacetic acid or hydrogen chloride in an inert organic solvent such as dichloromethane.

Novel compounds of formulae (XIII) are further embodiments of the invention.

Scheme 6 illustrates an alternative route for the preparation of a single enantiomer of the pyrrolidine acid intermediate of general formula (IV) from unsaturated intermediates of general formula (VII), using an oxazolidinone as a chiral auxiliary. The acid of formula (VIII) may be obtained by deprotection of (VII) and then converted to a mixed anhydride and coupled to an oxazolidinone (where R^4 is preferably phenyl, tertiary butyl, or iso-propyl) to provide an intermediate of formula (XIV). Alternatively, the reaction of a compound of formula (VII) (e.g. when PG^2 = OCO*t*-Bu) with the lithium salt of an oxazolidinone, in a suitable solvent (e.g. THF), may also provide a compound of formula (XIV).

The compound of formula (XIV) will undergo an [3+2]-azomethine ylide cycloaddition by reaction with the compound of general formula (XII), to provide diastereomers (XV) and (XVI) which can be separated by chromatography or crystallisation and hydrolysed to give a pyrrolidine of formula (IV). Alternatively, a compound of general formula (XVI) can be converted to a compound of general formula (XIII), for example by treatment with sodium methoxide in dimethyl carbonate (when PG^2 = OMe).

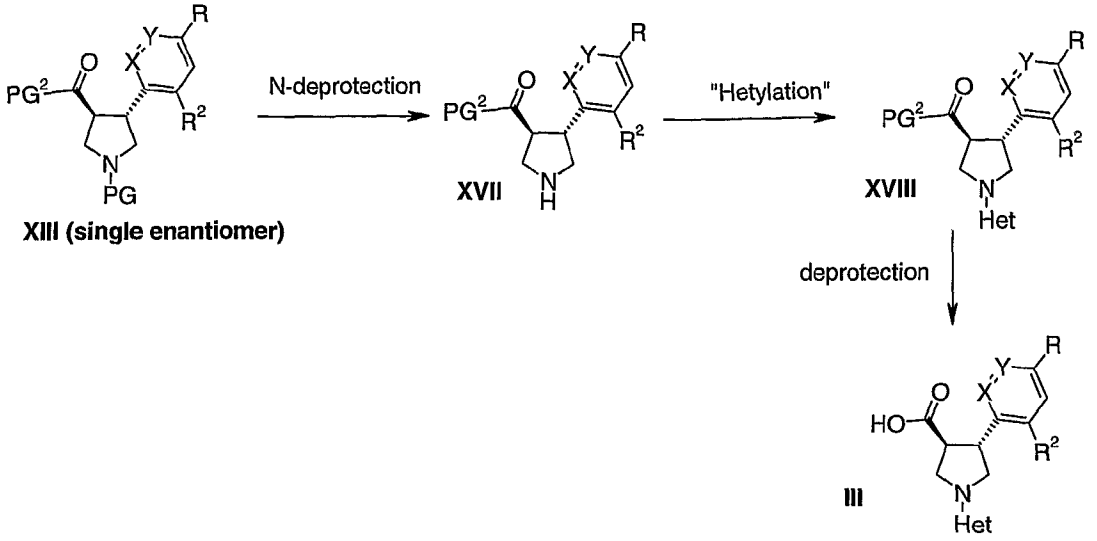


Scheme 6

PG is selected from suitable nitrogen protecting groups. PG^2 is selected from suitable carboxylic acid protecting groups, and different groups may be employed with respect to compounds (VII) and (XIII).

Novel compounds of formulae (XVI) are further embodiments of the invention.

Scheme 7 illustrates a route for preparation of the pyrrolidine acid intermediates of general formula (III) from intermediates of general formula (XIII). Once the protecting group PG is removed, using any suitable conventional techniques, Het groups may be introduced by suitable methods described above re Scheme 2. Removal of the acid protecting group PG^2, as described in scheme 4, then provides the acid of general formula (III).

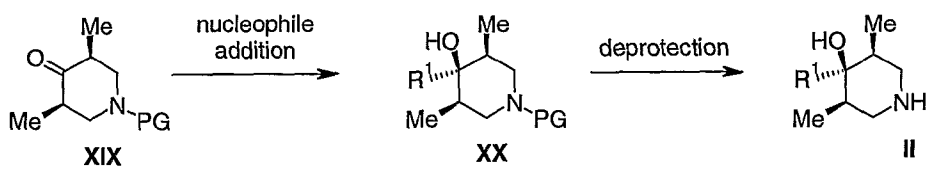


Scheme 7

PG is selected from suitable nitrogen protecting groups. PG^2 is selected from suitable carboxylic acid protecting groups.

Novel compounds of formulae (XVII) and (XVIII) are further embodiments of the invention.

As illustrated in Scheme 8, piperidine intermediates of general formula (II) can be prepared by addition of organometallic nucleophiles to ketones of general formula (XIX) containing a suitable nitrogen protecting group (PG) to furnish intermediates of general formula (XX). The stereochemistry of the addition is favoured such that the hydroxyl group in the product is *cis* to the two methyl groups. Controlled addition to carbonyl systems such as this have been described in the literature (e.g. Journal of Medicinal Chemistry (1964), 7(6), pp 726-8). Such nucleophilic addition is generally carried out at low temperature in an anhydrous ethereal or other non-polar solvent, using Grignard, organolithium or other suitable organometallic reagent. These organometallic reagents can be made by halogen-metal exchange using a suitable halide precursor, R^1-Br or R^1-I and *n*-butyl lithium or *t*-butyl lithium. Suitable protecting groups include benzyl, which may be removed by hydrogenation, or Boc, which may be removed by treatment with an acid such as TFA, or *para*-methoxybenzyl (PMB) which may be removed by treatment with DDQ, CAN or 1-chloroethyl chloroformate, to afford the desired piperidine intermediates of general formula (II). With certain protecting groups and under certain conditions the protecting group may be labile to treatment with the organometallic reagent, and so both transformations may be accomplished in one step. e.g. when PG = Boc the protecting group may sometimes be cleaved when intermediates of formula (XIX) are treated with an organometallic reagent.



Scheme 8

PG is selected from suitable nitrogen protecting groups.

The skilled man will appreciate that, in addition to protecting nitrogen or acid groups, as discussed hereinbefore, at various times during the synthesis of the compounds of formula I, it may be necessary to protect further groups, such as for example, hydroxy groups with a suitable protecting group, then remove the protecting group. Methods for deprotection of any particular group will depend on the protecting group. For examples of protection/ deprotection methodology see "Protective groups in Organic synthesis", TW Greene and PGM Wutz. For example, where a hydroxy group is protected as a methyl ether, deprotection conditions could for example comprise refluxing in 48% aqueous HBr, or by stirring with borane tribromide in dichloromethane. Alternatively where a hydroxy group is protected as a benzyl ether, deprotection conditions could for example comprise hydrogenation with a palladium catalyst under a hydrogen atmosphere.

All of the above reactions and the preparations of novel starting materials used in the preceding methods are conventional and appropriate reaction conditions for their performance or preparation as well as procedures for isolating the desired products will be well-known to those skilled in the art with reference to literature precedents and the Examples and Preparations herein.

A pharmaceutically acceptable salt of a compound of the formula (I) may be readily prepared by mixing together solutions of a compound of the formula (I) and the desired acid as appropriate. The salt may precipitate from solution and be collected by filtration or may be recovered by evaporation of the solvent. Pharmaceutically acceptable salts of compounds of formula (I) may be prepared by one or more of three methods:

(i) by reacting the compound of formula (I) with the desired acid;

(ii) by removing an acid- or base-labile protecting group from a suitable precursor of the compound of formula (I) or by ring-opening a suitable cyclic precursor, for example, a lactone or lactam, using the desired acid; or

(iii) by converting one salt of the compound of formula (I) to another by reaction with an appropriate acid or by means of a suitable ion exchange column.

All three reactions are typically carried out in solution. The resulting salt may precipitate out and be collected by filtration or may be recovered by evaporation of the solvent. The degree of ionisation in the resulting salt may vary from completely ionised to almost non-ionised.

The compounds of formula (I) of the present invention have utility as MCR4 agonists in the treatment of various disease states. Preferably said MCR4 agonists exhibit a functional potency at the MC4 receptor expressed as an EC_{50}, lower than about 1000nM, more preferably lower than 500nM, yet more preferably lower than about 100nM and more preferably still lower than about 50nM wherein said EC_{50} measurement of MCR4 functional potency can be carried out using Protocol E as described in International Patent Application publication number WO 2005/077935. Using this assay, compounds according to the present invention exhibit a functional potency at the MC4 receptor expressed as an EC_{50} lower than 1000nM.

Preferred compounds herein exhibit functional potency at the MCR4 receptor as defined herein before and are selective for MCR4 over MCR1. Preferably said MCR4 agonists have a selectivity for MCR4 over MCR1 wherein said MCR4 receptor agonists are at least about 10-times, preferably at least about 20-times, more preferably at least about 30-times, even more preferably at least about 100-times, more preferably still at least about 300-times, even more preferably still at least about 500-times and especially at least about 1000-times more functionally selective for a MCR4 receptor as compared with the MCR1 receptor wherein said relative selectivity assessments are based on the measurement of MCR1 and MCR4 functional potencies which can be carried out using the assays as described herein.

Preferably said MCR4 agonists have a selectivity for MCR4 over MCR3 wherein said MCR4 receptor agonists are at least about 10-times, preferably at least about 30-times, more preferably at least about 100-times, more preferably still at least about 300-times, even more preferably still at least about 500-times and especially at least about 1000-times more functionally selective for a MCR4 receptor as compared with the MCR3 receptor wherein said relative selectivity assessments are based on the measurement of MCR3 and MCR4 functional potencies which can be carried out using the assays as described herein.

Preferred compounds herein exhibit functional potency at the MCR4 receptor as defined herein before and are selective for MCR4 over MCR5. Preferably said MCR4 agonists have a selectivity for MCR4 over MCR5 wherein said MCR4 receptor agonists are at least about 10-times, preferably at least about 30-times, more preferably at least about 100-times, more preferably still at least about 300-times, even more preferably still at least about 500-times and especially about 1000-times more functionally selective for a MCR4 receptor as compared with the MCR5 receptor wherein said relative selectivity assessments are based on the measurement of MCR5 and MCR4 functional potencies which can be carried out using the assays as described herein.

Preferably said MCR4 agonists have a selectivity for MCR4 over MCR1 and MCR3 wherein said MCR4 receptors agonists are at least about 10-times, preferably at least about 30-times, more preferably at least about 100-times, more preferably still at least about 300-times, even more preferably still at least about 1000-times more functionally selective for a MCR4 receptor as compared with the MCR1 and MCR3 receptors.

Preferred compounds herein exhibit functional potency at the MCR4 receptor as defined herein before and are selective for MCR4 over MCR1 and MCR5. Preferably said MCR4 agonists have a selectivity for MCR4 over MCR1 and MCR5 wherein said MCR4 receptor agonists are at least about 10-times, preferably at least about 30-times, more preferably at least about 100-times, more preferably still at least about 300-times, even more preferably still at least about 500-times and especially at least about 1000-times more functionally selective for a MCR4 receptor as compared with the MCR1 and MCR5 receptors.

Preferably said MCR4 agonists have a selectivity for MCR4 over MCR3 and MCR5 wherein said MCR4 receptor agonists are at least about 10-times, preferably at least about 30-times, more preferably at least about 100-times, more preferably still at least about 300-times, most preferably at least about 1000-times more functionally selective for a MCR4 receptor as compared with the MCR3 and MCR5 receptors.

Combination therapy

The compounds of formula (I) or their salts, solvates or prodrugs, of the present invention may be usefully delivered in combination with an auxiliary effective active agent for the treatment of conditions of interest, such as sexual dysfunction, lower urinary tract disorders, obesity and/or diabetes. Further, the compounds of formula (I) or their salts, solvates or prodrugs, of the present invention may in some cases be usefully delivered in combination with an auxiliary effective active agent for the reduction of emesis. Some suitable auxiliary active agents which may be of use in combinations of the present invention include:

1) Compounds which modulate the action of natriuretic factors in particular atrial naturetic factor (also known as atrial naturetic peptide), B type and C type natriuretic factors such as inhibitors or neutral endopeptidase and in particular the compounds described and claimed in WO 02/02513, WO 02/03995, WO 02/079143 and EP-A-1258474 , and especially the compound of Example 22 of WO 02/079143 (2S)-2{[1-{3-4(-chlorophenyl)propyl]amino}carbonyl)- cyclopentyl]methyl}-4-methoxybutanoic acid;

2) Compounds which inhibit angiotensin-converting enzyme such as enalapril, and combined inhibitors of angiotensin-converting enzyme and neutral endopeptidase such as omapatrilat;

3) Substrates for NO-synthase, such as L-arginine;

4) Cholesterol lowering agents such as statins (e.g. atorvastatin/ Lipitor™) and fibrates;

5) Estrogen receptor modulators and/or estrogen agonists and/or estrogen antagonists, preferably raloxifene or lasofoxifene ((-)-cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydronaphthalene-2-ol, and pharmaceutically acceptable salts thereof the preparation of which is detailed in WO 96/21656);

6) A PDE inhibitor, more particularly a PDE 2, 3, 4, 5, 7 or 8 inhibitor, preferably PDE2 or PDE5 inhibitor and most preferably a PDE5 inhibitor (see hereinafter), said inhibitors preferably having an IC50 against the respective enzyme of less than 100nM (with the proviso that PDE 3 and 4 inhibitors are only administered topically or by injection to the penis for treatment of Male Erectile Dysfunction);

7) Vasoactive intestinal protein (VIP), VIP mimetic, VIP analogue, more particularly mediated by one or more of the VIP receptor subtypes VPAC1,VPAC or PACAP (pituitory adenylate cyclase activating peptide), one or more of a VIP receptor agonist or a VIP analogue (e.g. Ro-125-1553) or a VIP fragment, one or more of a α-adrenoceptor antagonist with VIP combination (e.g. Invicorp, Aviptadil);

8) A serotonin receptor agonist, antagonist or modulator, more particularly agonists, antagonists or modulators for 5HT1A (including VML 670 [WO02/074288] and flibanserin [US2003/0104980]), 5HT2A, 5HT2C, 5HT3 and/or 5HT6 receptors, including those described in WO-09902159, WO-00002550 and/or WO-00028993;

9) A testosterone replacement agent (including dehydroandrostendione), testosterone (e.g. Tostrelle™, LibiGel™), dihydrotestosterone or a testosterone implant;

10) Selective androgen receptor modulators e.g. LGD-2226;

11) Estrogen, estrogen and medroxyprogesterone or medroxyprogesterone acetate (MPA) (i.e. as a combination), or estrogen and methyl testosterone hormone replacement therapy agent (e.g. HRT especially Premarin, Cenestin, Oestrofeminal, Equin, Estrace, Estrofem, Elleste Solo, Estring, Eastraderm TTS, Eastraderm Matrix, Dermestril, Premphase, Preempro, Prempak, Premique, Estratest, Estratest HS, Tibolone);

12) A modulator of transporters for noradrenaline, dopamine and/or serotonin, such as bupropion, GW-320659;

13) An agonist or modulator for oxytocin/vasopressin receptors, preferably a selective oxytocin agonist or modulator;

14) An agonist or modulator for dopamine receptors, preferably a D3 or D4 selective agonist or modulator e.g. apomorphine; and

15) An antiemetic agent, for example a 5-HT_3 antagonist or a neurokinin-1 (NK-1) antagonist.
Suitable 5-HT_3 antagonists include, but are not limited to, granisetron, ondansetron, tropisetron, ramosetron, palonsetron, indisetron, dolasetron, alosetron and azasetron.
Suitable NK-1 antagonists include, but are not limited to, aprepitant, casopitant, ezlopitant, cilapitant, netupitant, vestipitant, vofopitant and 2-(R)-(1-(R)-3,5-bis(trifluoromethyl)phenyl)ethoxy-4-(5-

(dimethylamino)methyl-1,2,3-triazol-4-yl)methyl-3-(S)-(4-fluorophenyl)morpholine. See for example International Patent Application publication number WO2006/049933.

With particular reference to the use of the compounds of the invention for the treatment of lower urinary tract dysfunction, combinations with other agents may include but are not limited to

- Muscarinic acetylcholine receptor antagonist such as tolterodine;
- Alpha adrenergic receptor antagonist, in particular an alpha1 adrenergic receptor antagonist or an alpha2 adrenergic receptor antagonist;
- Alpha adrenergic receptor agonist or partial agonist, in particular an alpha1 adrenergic receptor agonist or partial agonist, or an alpha2 adrenergic receptor agonist or partial agonist;
- 5HT2C agonist (see WO 2004/096196);
- Serotonin and Noradrenalin reuptake inhibitor (SNRI);
- Noradrenalin reuptake inhibitor (NRI) such as reboxetine, either in its racemic or (S,S)-enantiomeric form;
- Vanilloid receptor (VR) antagonist, such as capsaicin;
- alpha2delta ligand, such as gabapentin or pregabalin;
- Beta3 adrenergic receptor agonist;
- 5HT1a receptor antagonist or 5HT1a receptor inverse agonist;
- Prostanoid receptor antagonist, e.g. EP1 receptor antagonist.

With regard to the use of the compounds of formula (I) in the treatment of obesity and related disorders, the compounds may also be useful in conjunction with other anti-obesity agents. Suitable anti-obesity agents include cannabinoid 1 (CB-1) receptor antagonists (such as rimonabant), apolipoprotein-B secretion/microsomal triglyceride transfer protein (apo-B/MTP) inhibitors (in particular, gut-selective MTP inhibitors, such as edipatapide or dirlotapide), 11β-hydroxy steroid dehydrogenase-1 (11β-HSD type 1) inhibitors, peptide YY_{3-36} and analogs thereof, cholecystokinin-A (CCK-A) agonists, monoamine reuptake inhibitors (such as sibutramine), sympathomimetic agents, β_3 adrenergic receptor agonists, dopamine receptor agonists (such as bromocriptine), melanocyte-stimulating hormone receptor analogs, 5HT2c receptor agonists, melanin concentrating hormone antagonists, leptin (the OB protein), leptin analogs, leptin receptor agonists, galanin antagonists, lipase inhibitors (such as tetrahydrolipstatin, i.e. orlistat), anorectic agents (such as a bombesin agonist), Neuropeptide-Y receptor antagonists (in particular, NPY-5 receptor antagonists), thyromimetic agents, dehydroepiandrosterone or an analog thereof, glucocorticoid receptor agonists or antagonists, orexin receptor antagonists, glucagon-like peptide-1 receptor agonists, ciliary neurotrophic factors (such as Axokine™ available from Regeneron Pharmaceuticals, Inc., Tarrytown, NY and Procter & Gamble Company, Cincinnati, OH), human agouti-related protein (AGRP) inhibitors, ghrelin receptor antagonists, histamine 3 receptor antagonists or inverse agonists, neuromedin U receptor agonists and the like. Other anti-obesity agents, including the preferred agents set forth hereinbelow, are well known, or will be readily apparent in light of the instant disclosure, to one of ordinary skill in the art. The compounds of the present invention may also be administered in combination with a naturally occurring compound that acts to lower plasma cholesterol

levels. Such naturally occurring compounds are commonly called nutraceuticals and include, for example, garlic extract, *Hoodia* plant extracts, and niacin. Especially preferred are anti-obesity agents selected from the group consisting of CB-1 antagonists, gut-selective MTP inhibitors, orlistat, sibutramine, bromocriptine, ephedrine, leptin, peptide YY_{3-36} and analogs thereof, and pseudoephedrine. Preferably, compounds of the present invention and combination therapies for the treatment of obesity and related conditions are administered in conjunction with exercise and a sensible diet. Preferred CB-1 antagonists include Rimonabant (SR141716A also known under the tradename Acomplia™ available from Sanofi-Synthelabo) described in U.S. Patent No. 5,624,941; and compounds described in U.S. Patent Nos. 5,747,524, 6,432,984 and 6,518,264; U.S. Patent Publication Nos. US2004/0092520, US2004/0157839, US2004/0214855, and US2004/0214838; U.S. Patent Application Serial No. 10/971599 filed on October 22, 2004; and PCT Patent Publication Nos. WO 02/076949, WO 03/075660, WO04/048317, WO04/013120, and WO 04/012671. Preferred gut-slective MTP inhibitors include dirlotapide described in U.S. Patent No. 6,720,351; 4-(4-(4-(4-((2-((4-methyl-4H-1,2,4-triazol-3-ylthio)methyl)-2-(4-chlorophenyl)-1,3-dioxolan-4-yl)methoxy)phenyl)piperazin-1-yl)phenyl)-2-*sec*-butyl-2H-1,2,4-triazol-3(4H)-one (R103757) described in U.S. Patent Nos. 5,521,186 and 5,929,075; and implitapide (BAY 13-9952) described in U.S. Patent No. 6,265,431. Other representative anti-obesity agents for use in the combinations, pharmaceutical compositions, and methods of the invention can be prepared using methods known to one of ordinary skill in the art, for example; sibutramine can be prepared as described in U.S. Pat. No. 4,929,629; bromocriptine can be prepared as described in U.S. Pat. Nos. 3,752,814 and 3,752,888; orlistat can be prepared as described in U.S. Pat. Nos. 5,274,143; 5,420,305; 5,540,917; and 5,643,874; and PYY_{3-36} (including analogs) can be prepared as described in US Publication No. 2002/0141985 and WO 03/027637.

One preferred group herein are combinations of the compounds of the present invention and one or more additional therapeutic agents selected from: PDE5 inhibitors; NEP inhibitors; D3 or D4 selective agonists or modulators; estrogen receptor modulators and/or estrogen agonists and/or estrogen antagonists; testosterone replacement agents, testosterone or a testosterone implant; estrogen, estrogen and medroxyprogesterone or medroxyprogesterone acetate (MPA), or estrogen and methyl testosterone hormone replacement therapy agent.

Preferred combinations for the treatment of MED are combinations of the compounds of the present invention and one or more PDE5 inhibitors and/or NEP inhibitors.

Preferred combinations for the treatment of FSD are combinations of the compounds of the present invention and PDE5 inhibitors, and/or NEP inhibitors, and/or D3 or D4 selective agonists or modulators, and/or estrogen receptor modulators, estrogen agonists, estrogen antagonists, and/or testosterone replacement agents, testosterone, testosterone implant, and/or estrogen, estrogen and medroxyprogesterone or medroxyprogesterone acetate (MPA), estrogen and methyl testosterone hormone replacement therapy agent.

Particularly preferred PDE5 inhibitors for such combined products for the treatment of MED or FSD are 5-[2-ethoxy-5-(4-methyl-1-piperazinylsulphonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (sildenafil, particularly present as the citrate salt); (6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione (IC-351 or tadalafil); 2-[2-ethoxy-5-(4-ethyl-piperazin-1-yl-1-sulphonyl)-phenyl]-5-methyl-7-propyl-3H-imidazo[5,1-f][1,2,4]triazin-4-one (vardenafil); 5-(5-Acetyl-2-butoxy-3-pyridinyl)-3-ethyl-2-(1-ethyl-3-azetidinyl)-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one; 5-(5-Acetyl-2-propoxy-3-pyridinyl)-3-ethyl-2-(1-isopropyl-3-azetidinyl)-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one; 5-[2-ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-2-[2-methoxyethyl]-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one; 4-[(3-chloro-4-methoxybenzyl)amino]-2-[(2S)-2-(hydroxymethyl)pyrrolidin-1-yl]-N-(pyrimidin-2-ylmethyl)pyrimidine-5-carboxamide (TA-1790); 3-(1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-N-[2-(1-methylpyrrolidin-2-yl)ethyl]-4-propoxybenzenesulfonamide (DA 8159) and pharmaceutically acceptable salts thereof.

Particularly preferred NEP inhibitors for such combined products for the treatment of MED or FSD are the compounds exemplified in WO 02/079143.

By cross reference herein to compounds contained in patents and patent applications which can be used in accordance with invention, we mean the therapeutically active compounds as defined in the claims (in particular of claim 1) and the specific examples (all of which is incorporated herein by reference).

If a combination of active agents is administered, then they may be administered simultaneously, separately or sequentially, in formulations which may be the same or different.

Biological Assays

Melanocortin receptor agonist activity; selectivity

Measurement of *in vitro* agonist potency (EC_{50}) of compounds against melanocortin receptors type 1 and 3 (MC1 and MC3).

Activation of melanocortin (MC) receptors by agonists results in activation of intracellular adenylate cyclase enzymes that synthesise the second messenger signalling molecule, adenosine 3',5'-cyclic monophosphate (cAMP). Changes in cAMP levels following treatment of recombinant MC1 and MC3 cell lines with test compound were measured and an MC1 and MC3 potency estimate (EC_{50}) calculated as follows:

Human embryonic kidney (HEK) or Chinese hamster ovary cell lines stably transfected with full length cDNA encoding human MC1 or MC3 receptors, respectively, were established using standard molecular biology methods. Test compounds were dissolved in dimethyl sulfoxide (DMSO) at 4mM. 11 point half log unit increment dilution series of test compound, typically starting at 50uM were prepared in a buffer

comprised of phosphate buffered saline (PBS), 2.5% DMSO and 0.05% pluronic F-127 surfactant. Freshly cultured cells at 80-90% confluence were harvested and re-suspended in Dulbecco's Modified Eagle's Medium (DMEM). Cells (10,000 for MC3, 20,000 for MC1) were added to the test compound dilution series in a 384 well assay plate and incubated for 1 hour at 37°C. The relative cAMP concentration in each well was then measured using a β- galactosidase enzyme fragment complementation method purchased in kit form as the Discoverx cAMP II kit from GE Healthcare / Amersham Biosciences UK. In the case of MC1, 3-Isobutyl-1-methylxanthine (IBMX) at a concentration of 750 μM was included in DMEM as the cells were re-suspended for assay. The fluorescence readings taken from each assay well were converted into percent effect relative to maximum control wells corresponding to a concentration of alpha melanocyte stimulating hormone demonstrated to give a maximal effect. Sigmoidal curves were fitted to plots of $\log_{10}$ inhibitor concentration *vs* percent effect using a custom made software application called SIGHTS and EC_{50} estimates determined by the software as the concentration of test compound giving an effect half way between the bottom and top assymptopes of the sigmoidal dose response curve. Each experiment included an EC_{50} determination for alpha melanocyte stimulating hormone, which was used as a standard to track assay consistency and allow fair comparison between EC_{50} estimates obtained in different experiments.

MC5 and MC4 EC_{50} activity was determined as described by assay protocols D and E, respectively, in US2005/0176772 (pages 28-30).

Nle4, D-Phe7-α-MSH Inhibition at the MC4 Receptor

Nle4, D-Phe7-α-MSH is a stable analogue of melanocyte-stimulating hormone (MSH), which is an agonist at the MC4 receptor (MC4R). Compounds can be evaluated for their ability to inhibit Nle4, D-Phe7-α-MSH binding to membranes from cells expressing the MC4R using a competition binding assay versus [^{125}I] Nle4, D-Phe7-α–MSH.

Cells expressing the MC4R were subject to homogenisation and the membrane fragment isolated by differential centrifugation. CHO-CRE MC4R cell membranes were coupled to PVT-PEI-WGA SPA Beads type A for 2 hours, spun at 1000 RPM for 5 mins and suspended to a concentration of 300ug bead/ml (0.15ug membrane, 15ug bead per well). Bead/membrane mix was incubated with 0.06nM [^{125}I] Nle4, D-Phe7-α–MSH and 11 half-log concentrations of competitor ligand, in duplicate, in a total volume of 50μl buffer per well (25 mM HEPES, 1mM $MgCl_2$, 2.5 mM $CaCl_2$, 1% Pluronic F68, 1 complete EDTA protease inhibitor tablet/50 ml pH7). Non-specific binding was determined by the inclusion of 100nM SHU9119. The reaction was initiated by the addition of bead/membranes and plates were incubated at room temperature for 12 hours (the first hour on a plate shaker), after which the amount of radioactivity present was determined using a Wallac plate counter. Ki values were determined by data analysis using appropriate software.

Preferably the compounds of the present invention exhibit a binding constant at the MC4 receptor expressed as an Ki value against Nle4, D-Phe7-α-MSH of lower than about 1000nM, more preferably

lower than 500nM, yet more preferably lower than about 100nM and more preferably still lower than about 50nM, wherein said Ki value is determined using the assay described above.

Nle4, D-Phe7-α-MSH Inhibition at the MC3 receptor

Nle4, D-Phe7-α-MSH is a stable analogue of melanocyte-stimulating hormone (MSH), which is an agonist at the MC3 receptor (MC3R). Compounds can be evaluated for their ability to inhibit Nle4, D-Phe7-α-MSH binding to membranes from cells expressing the MC3R using a competition binding assay versus [^{125}I] Nle4, D-Phe7-α–MSH.

Cells expressing the MC3R were subject to homogenisation and the membrane fragment isolated by differential centrifugation. CHO-CRE MC3R cell membranes were coupled to PVT-PEI-WGA SPA Beads type A for 2 hours, spun at 1000 RPM for 5 mins and suspended to a final assay concentration of 800ug bead/ml (1.2ug membrane, 40ug bead per well). Bead/membrane mix was incubated with 0.06nM [^{125}I] Nle4, D-Phe7-α–MSH and 11 half-log concentrations of competitor ligand, in duplicate, in a total volume of 50µl buffer per well (25 mM HEPES, 1mM $MgCl_2$, 2.5 mM $CaCl_2$, 1% Pluronic F68, 1 complete EDTA protease inhibitor tablet/50 ml pH7). Non-specific binding was determined by the inclusion of 100nM SHU9119. The reaction was initiated by the addition of bead/membranes and plates were incubated at room temperature for 12 hours (the first hour on a plate shaker), after which the amount of radioactivity present was determined using a Wallac plate counter. Ki values were determined by data analysis using appropriate software.

High Density Drug-Drug Interactions (DDI) 3µM Cocktail Screen

A drug interaction is a situation in which a substance affects the activity of another drug, i.e. the effects are increased or decreased, or together they produce a new effect that neither produces on its own. Drug interactions may be the result of various processes but a relatively common one is where one drug affects the pharmacokinetics of another by inhibiting the cytochrome P450 that metabolises it. Because of the importance of these phenomena, assessment of the DDI potential for new chemical entities (NCEs) is considered important early on in the drug discovery process.

The DDI cocktail screen in human liver microsomes (HLM) is run in a fully automated fashion and the aim of the screen is to provide a single-point assessment of the DDI potential of new chemical entity (NCE; tested at 3 µM) against the 4 primary cytochrome P450 enzymes, 1A2, 2D6, 2C9 and 3A4.

The substrate cocktail approach for P450 DDI utilizes human liver microsomes together with isoform-specific clinical drug probes and permits the simultaneous measurement of the inhibition of P450 1A2, 2C9, 2D6 & 3A4 activities in a single incubation. This is run in high throughput with simultaneous detection of metabolites by LC-MS/MS. This method has been thoroughly tested and evaluated using standard compounds. The probe substrates used are given in the table below.

Microsome Source	Pooled human liver microsomes,
Microsome Concentration	0.1 mg/mL
P450 Concentration	0.03 μM
Regeneration System	NADPH (1.3 mM)
Assay Time	8 min
Probe Substrate (Enzyme Probed)	Concentration
Tacrine (1A2)	2 μM
Diclofenac (2C9)	5 μM
Dextromethorphan (2D6)	5 μM
Midazolam (3A4)	2 μM
Inhibitors	Concentration
NCE (test compound)	3 μM
Miconazole (universal control)	3 μM

Appearance of the metabolite of each substrate is measured over time in the presence and absence of the NCE (test compound/inhibitor) at a concentration of 3 μM. The compounds are assessed for their inhibitory potential as a percentage value and interpreted using the following scheme. These data are then used in conjunction with other measurements to evaluate the suitability of NCEs and to help with the design and progression of compounds.

% Inhibition	IC50
> 75%	< 1 μM
25-75%	1-10 μM
< 25%	> 10 μM

AGRP Inhibition

Agouti related protein (AGRP) is a high affinity endogenous antagonist/inverse agonist for the MC4 receptor (Lu et al., 1994, *Nature* 371: 799-802; Ollman et al., 1997, *Science* 278: 135-138). AGRP levels are upregulated by fasting (Mizuno & Mobbs 1999, *Endocrinology*. 140: 4551-4557) and therefore it is important to assess the ability of anti-obesity agents acting through the MC4 receptor to inhibit the binding of AGRP. It has been ascertained that this C-terminal fragment of AGRP contains the MC4R binding determinants (Yang et al., 1999, *Mol Endocrinol* 13: 148-155), therefore, compounds can be evaluated for their ability to inhibit AGRP binding to membranes from cells expressing the MC4R using a competition binding assay versus [^{125}I]AGRP(87-132). To this end cells expressing the MC4R were subject to homogenisation and the membrane fragment isolated by differential centrifugation. CHO-CRE MC4R cell membranes (12μg protein) were incubated with 0.3nM [^{125}I]AGRP(87-132) and 11 half-log concentrations of competitor ligand, in duplicate, in a total volume of 100μl buffer (25mM HEPES, 1mM

$MgCl_2$, 2.5mM $CaCl_2$, 0.5% BSA pH 7.0). Non-specific binding was determined by the inclusion of 1μM SHU9119. The reaction was initiated by the addition of membranes and plates were incubated at room temperature for 2 hours. The reaction was terminated by rapid filtration onto GF/C filters (presoaked in 1% PEI) using a vacuum harvester followed by five 200μl washes of ice cold wash buffer (Binding buffer containing 500mM NaCl). The filters were soaked in 50μl scintillation fluid and the amount of radioactivity present was determined by liquid scintillation counting. Ki values were determined by data analysis using appropriate software.

Preferably the compounds of the present invention exhibit a binding constant at the MC4 receptor expressed as an Ki value against AGRP of lower than about 1000nM, more preferably lower than 500nM, yet more preferably lower than about 100nM and more preferably still lower than about 50nM, wherein said Ki value is determined using the assay described above. Using this assay, compounds according to the present invention exhibit a binding constant at the MC4 receptor expressed as an Ki value against AGRP lower than 1000nM.

Food Intake Study: To assess the efficacy of an MC4 agonist on food intake and body weight over a 24 hour period in the male rat

Rats will be acclimatised to single housing and reverse lighting conditions (9.30am - 9.30pm) for approximately two weeks before the start of the study. Rats will be acclimatised to the Techincal Scientific Equipment* (TSE) cages approximately 24 hours prior to the study day. Rats will be randomly assigned to a treatment group on the morning of the study based on its weight (n=5/treatment). Each rat will either receive the MC4 agonist or vehicle orally just before lights go out. Following dosing the rat will be immediately placed back in to the TSE cage and food intake and water consumption will be monitored throughout the course of the study (24 hours). Locomotor activity will also be monitored in the form of light beam breaks.
At the end of the study rats will be killed by exsanguination under terminal anaesthesia by Isoflurane. Blood will be removed from the rat by cardiac puncture and analysed for drug concentration levels and biomarkers.

The data are expressed as mean ± SEM and comparisons between the control and the treatment is analysed by ANOVA. Statistical significance is accepted at a level of $p<0.05$.

In vitro Metabolism Rate Determination (Human Liver Microsome (HLM); Rat Liver Microsome (RLM) Assay)

Many drugs are metabolised by the cytochrome P450 mono-oxygenase system. This enzyme is found in high concentrations in the liver and is bound to the endoplasmic reticulum of the hepatocyte. The enzyme system can be obtained in semi-purified state by the preparation of the hepatic microsomal fractions. Determining a compound's *in vitro* half-life in such a system provides a useful indicator of metabolic stability.

Materials And Reagents

All reagents are ANALAR grade.

1. 200mM Phosphate buffer (Sigma) - 100ml 1M Phosphate buffer pH7.4 dissolved with 400ml MilliQ water. If necessary, pH should be adjusted with concentrated orthophosphoric acid to pH 7.4, made up monthly and stored refrigerated (2-8°C).

2. 0.1M $MgCl_2.6H_2O$ (BDH) - 2.032g dissolved in 100ml MilliQ water, and stored refrigerated (2-8°C).

3. 0.02M NADP (Sigma) - 15.3mg dissolved in 1000µl MilliQ water - and then stored refrigerated (2-8°C) for further use.

4. 0.1M D-L Isocitric acid (Sigma) - 129mg dissolved in 5ml MilliQ water - and then stored refrigerated (2-8°C) for further use.

5. Isocitric dehydrogenase, Type IV (Sigma) – stored refrigerated (2-8°C).

6. Stock solution of substrate (approximately 1mg/ml) in miscible organic solvents such as methanol, ethanol or water, stored refrigerated (2-8°C).

7. 50mM p-Nitroanisole (PNA) (Aldrich) – 7.65mg dissolved in 1ml methanol, and stored refrigerated (2-8°C) until ready for use.

8. 50µM p-Nitrophenol (PNP) (Sigma) - 0.69mg dissolved in 100ml water and stored refrigerated (2-8°C).

9. 20% Trichloroacetic acid (TCA) (BDH) - 20g dissolved in 100ml MilliQ water, made up in amber glassware and stored at room temperature.

10. 10M Sodium hydroxide (BDH) - 40g dissolved in 100ml MilliQ water (care should be exercised when preparing this solution as this reaction is exothermic), made up in "safebreak" glassware and stored at room temperature.

11. Hepatic or Supermix microsomes stored at -80°C should be defrosted immediately prior to use, kept on ice and dispensed.

12. MilliQ water.

13 .Thermostatically controlled shaking water bath set to give a temperature in the incubation of approx 37°C.

14. Reagent for termination of incubation (typically organic solvent, acid or base).

Methodology For *In Vitro* Rate Determination Using Hepatic & Supermix Microsomes

The method outlined below is for a total incubation volume of 1.5ml.

1. The following mixture is prepared in a test tube:

Reagent	Stock concentration	Concentration in incubation	Volume added (for 1.5ml incubation)
Phosphate buffer pH 7.4	200mM	50mM	375µl
$MgCl_2$	0.1M	5mM	75µl
Isocitric acid	0.1M	5mM	75µl
Isocitric dehydrogenase	on bottle	1 unit per ml *	see below*

*This volume is calculated for each new batch of isocitric dehydrogenase

e.g. Protein concentration = 18mg/ml

Enzyme activity = 3.3 units/mg

therefore Specific activity = 3.3 x 18 units/ml = 59 units/ml

For a 1.5ml incubation 1.5 units of enzyme activity are required = $\frac{1.5}{59}$ x 1000 = 25.4µl.

2. Defrost microsomes at room temperature and add sufficient microsomes to give a final concentration of 0.5nmol cytochrome P450/ml of incubation e.g. for a 1.5 ml incubation, the volume of microsomes to be added is:

$$\frac{\text{P450 concentration required in incubation x incubation volume}}{\text{cytochrome P450 concentration in microsomal prep.}}$$

3. Add sufficient MilliQ water to give a total incubation volume of 1.425ml.

4. Remove 237.5µl of incubation mix and place in test tube for PNA positive control. Add 2.5µl of PNA solution, whirlimix, and put tube into a rack in the thermostatically controlled shaking water bath

5. Remove 100µl for no substrate control and dispense in test tube. Place test tube in a rack in the thermostatically controlled shaking water bath.

6. Add substrate to the incubation. The substrate should be at an initial concentration of 1µM. The volume of substrate required in the remaining 1.162.5ml incubation is calculated as follows:

$$\frac{\text{RMM x incubation vol. x initial conc. in incubation}}{\text{1000 x stock substrate solution conc.}}$$

N.B. The volume of organic solvent added should not exceed 0.1% of the total incubation volume.

7. Remove 100µl of incubation mix into test tube for no cofactor control. Whirlimix and put into a rack in the thermostatically controlled shaking water bath.

8. Pre-incubate the tube containing the incubation mix, also positive control and no cofactor tubes in the thermostatically controlled shaking water bath set at 37°C for approx 5 min.

9 .Add NADP to initiate reaction (75µl to each 1.162.5ml incubation mix, 12.5µl to positive control tube and 5µl to no substrate tube) and take first time point immediately. The PNA positive control, no cofactor control and no substrate tubes are incubated for the total incubation time.

10. Remove 100µl aliquots up to 9 different sampling points from 0 to 60 min (usually 0, 3, 5, 10, 15, 20, 30, 45 & 60 min) and terminate reaction. Longer incubation times can be used, but, after 120 min the microsomes deteriorate. The reaction may be terminated by addition of organic solvent, acid or base. At the end of the incubation process the no cofactor and no substrate controls in a similar manner i.e. terminate with the same reagent.

11. PNA positive control procedure:

After the final sample has been taken, remove the positive control and add 1ml 20% TCA to this tube. Also prepare a tube containing 250µl of a PNP standard at 50µM, and add 1ml 20% TCA. Whirlimix both tubes and leave for approx 5 min to allow the protein to precipitate.

Centrifuge both tubes for approx 5 min in an instrument set at 3500rpm. Remove 1ml of supernatant and place into clean test tubes, discard the remainder.

Add 1ml 10M NaOH to the supernatant, whirlimix, and leave to stand for approx 5 min. Blank spectrophotometer with distilled water at 400 nm then measure absorbance of the PNP standard against distilled water. The microsomal 4-nitroanisole O-demethylase activity is calculated as follows:

Calculation of results

$$\frac{\text{Absorbance sample} \times \text{nmoles PNP in standard (ie 12.5nmoles)}}{\text{Absorbance PNP std} \times 60 \times 0.125} = \text{nmoles/min/nmol P450}$$

The activity value from the incubation MUST be equal to or greater than 85% of the mean value of the batch used for the incubation to be valid. If this criteria is not met, then the incubation must be repeated.

11. Analyse samples (including no cofactor and no substrate control) by a specific assay for the substrate to determine the disappearance kinetics.

Analysis Of Data

Data obtained using the procedure described above can be quantified in terms of the substrates *in vitro* intrinsic clearance (Clint). Providing that the substrate concentration is below Km, the metabolism should be 1st order giving a log-linear plot of substrate disappearance with time.
The *in vitro* half-life of the substrate can be determined by plotting the natural logarithm (ln) of a measure of relative substrate concentration (e.g. drug/internal standard ratio) against time and fitting the line of best fit to this data. The gradient of this line is the first order rate constant (k) for the substrate disappearance and is determined by regression analysis. This rate constant can be converted to the half-life according to the following equation :-

$$\textit{in vitro}\ \text{half-life}\ (t_{1/2}) = -\frac{\mathrm{Ln2}}{k}$$

Alternatively the rate constant can be converted to an intrinsic clearance (Clint) according to the following equation:-

$$\text{Clint}\ (\mu\text{l/min/mg}) = (\mathbf{k}/\text{protein concentration in incubation (mg/ml)})^{*}1000$$

Preferably the compounds of the present invention exhibit a clearance, as determined by the above assay, expressed as a value of lower than about 200µL/min/mg, more preferably lower than 100µL/min/mg, yet more preferably lower than about 50 µL/min/mg and more preferably still lower than about 20µL/min/mg. Using this assay, compounds according to the present invention which have been tested exhibit a clearance lower than 200 µL/min/mg.

Administration Methods

Compounds of the invention intended for pharmaceutical use may be administered as crystalline or amorphous products. They may be obtained, for example, as solid plugs, powders, or films by methods such as precipitation, crystallization, freeze-drying, spray drying, or evaporative drying. Microwave or radio frequency drying may be used for this purpose.

They may be administered alone or in combination with one or more other compounds of the invention or in combination with one or more other drugs (or as any combination thereof). Generally, they will be administered as a formulation in association with one or more pharmaceutically acceptable excipients. The term 'excipient' is used herein to describe any ingredient other than the compound(s) of the

invention. The choice of excipient will to a large extent depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form.

Pharmaceutical compositions suitable for the delivery of compounds of the present invention and methods for their preparation will be readily apparent to those skilled in the art. Such compositions and methods for their preparation may be found, for example, in Remington's Pharmaceutical Sciences, 19th Edition (Mack Publishing Company, 1995).

Accordingly the present invention provides for a pharmaceutical composition comprising a compound of formula (I) and a pharmaceutically acceptable diluent or carrier.

Any suitable route of administration may be employed for providing a mammal, especially a human with an effective dosage of a compound of the present invention. For example, oral (including buccal and sublingual administration), rectal, topical, parental, ocular, pulmonary, nasal, and the like may be employed. Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, creams, ointments, aerosols, and the like. Preferably compounds of formula (I) are administered orally or intranasally.

The effective dosage of active ingredient employed may vary depending on the particular compound employed, the mode of administration, characteristics of the mammal to be treated (e.g. body weight), the condition being treated and the severity of the condition being treated. Such dosage may be ascertained readily by a person skilled in the art.

For the treatment of sexual dysfunction compounds of the present invention are given in a dose range of from about 0.001 milligram (mg) to about 1000 mg, preferably from about 0.001 mg to about 500 mg, more preferably from about 0.001 mg to about 100 mg, even more preferably from about 0.001 mg to about 50 mg and especially from about 0.002 mg to about 25 mg per kilogram of body weight, preferably as a single dose orally or as a nasal spray. For example, oral administration may require a total daily dose of from about 0.1 mg up to about 1000 mg, while an intravenous dose may only require from about 0.001 mg up to about 100 mg. The total daily dose may be administered in single or divided doses and may, at the physician's discretion, fall outside of the typical range given herein.

When treating obesity, in conjunction with diabetes and/or hyperglycemia, or alone, generally satisfactory results are obtained when the compounds of the present invention are administered at a daily dosage of from about 0.0001 mg to about 1000 mg, preferably about 0.001 mg to about 500 mg, more preferably about 0.005 mg to about 100 mg and especially about 0.005 mg to about 50 mg per kilogram of animal body weight, preferably given in a single dose or in divided doses two to six times a day, or in sustained release form. In the case of a 70 kg adult human, the total daily dose will generally be from about 0.7 mg up to about 3500 mg. This dosage regimen may be adjusted to provide the optimal therapeutic response.

When treating diabetes mellitus and/or hyperglycemia, as well as other diseases or disorders for which compounds of formula I are useful, generally satisfactory results are obtained when the compounds of the present invention are administered at a daily dosage of from about 0.001 mg up to about 100 mg per kilogram of animal body weight, preferably given in a single dose or in divided doses two to six times a day, or in sustained release form. In the case of a 70 kg adult human, the total daily dose will generally be from about 0.07 mg up to about 350 mg. This dosage regimen may be adjusted to provide the optimal therapeutic response.

These dosages are based on an average human subject having a weight of about 65kg to 70kg. The physician will readily be able to determine doses for subjects whose weight falls outside this range, such as infants, the elderly and the obese.

The compounds of the invention may be administered orally. Oral administration may involve swallowing, so that the compound enters the gastrointestinal tract, and/or buccal, lingual or sublingual administration by which the compound enters the blood stream directly from the mouth.

Formulations suitable for oral administration include solid, semi-solid and liquid systems such as tablets; soft or hard capsules containing multi- or nano-particulates, liquids, or powders; lozenges (including liquid-filled); chews; gels; fast dispersing dosage forms; films; ovules; sprays; and buccal/mucoadhesive patches.

Liquid formulations include suspensions, solutions, syrups and elixirs. Such formulations may be employed as fillers in soft or hard capsules (made, for example, from gelatin or hydroxypropylmethylcellulose) and typically comprise a carrier, for example, water, ethanol, polyethylene glycol, propylene glycol, methylcellulose, or a suitable oil, and one or more emulsifying agents and/or suspending agents. Liquid formulations may also be prepared by the reconstitution of a solid, for example, from a sachet. may also be prepared by the reconstitution of a solid, for example, from a sachet.

The compounds of the invention may also be used in fast-dissolving, fast-disintegrating dosage forms such as those described in Expert Opinion in Therapeutic Patents, 11 (6), 981-986 by Liang and Chen (2001).

For tablet dosage forms, depending on dose, the drug may make up from 1 wt% to 80 wt% of the dosage form, more typically from 5 wt% to 60 wt% of the dosage form. In addition to the drug, tablets generally contain a disintegrant. Examples of disintegrants include sodium starch glycolate, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, croscarmellose sodium, crospovidone, polyvinylpyrrolidone, methyl cellulose, microcrystalline cellulose, lower alkyl-substituted hydroxypropyl cellulose, starch, pregelatinised starch and sodium alginate. Generally, the disintegrant will comprise from 1 wt% to 25 wt%, preferably from 5 wt% to 20 wt% of the dosage form.

Binders are generally used to impart cohesive qualities to a tablet formulation. Suitable binders include microcrystalline cellulose, gelatin, sugars, polyethylene glycol, natural and synthetic gums, polyvinylpyrrolidone, pregelatinised starch, hydroxypropyl cellulose and hydroxypropyl methylcellulose. Tablets may also contain diluents, such as lactose (monohydrate, spray-dried monohydrate, anhydrous and the like), mannitol, xylitol, dextrose, sucrose, sorbitol, microcrystalline cellulose, starch and dibasic calcium phosphate dihydrate.

Tablets may also optionally comprise surface active agents, such as sodium lauryl sulfate and polysorbate 80, and glidants such as silicon dioxide and talc. When present, surface active agents may comprise from 0.2 wt% to 5 wt% of the tablet, and glidants may comprise from 0.2 wt% to 1 wt% of the tablet.

Tablets also generally contain lubricants such as magnesium stearate, calcium stearate, zinc stearate, sodium stearyl fumarate, and mixtures of magnesium stearate with sodium lauryl sulphate. Lubricants generally comprise from 0.25 wt% to 10 wt%, preferably from 0.5 wt% to 3 wt% of the tablet.

Other possible ingredients include anti-oxidants, colourants, flavouring agents, preservatives and taste-masking agents.

Exemplary tablets contain up to about 80% drug, from about 10 wt% to about 90 wt% binder, from about 0 wt% to about 85 wt% diluent, from about 2 wt% to about 10 wt% disintegrant, and from about 0.25 wt% to about 10 wt% lubricant.

Tablet blends may be compressed directly or by roller to form tablets. Tablet blends or portions of blends may alternatively be wet-, dry-, or melt-granulated, melt congealed, or extruded before tabletting. The final formulation may comprise one or more layers and may be coated or uncoated; it may even be encapsulated.

The formulation of tablets is discussed in Pharmaceutical Dosage Forms: Tablets, Vol. 1, by H. Lieberman and L. Lachman (Marcel Dekker, New York, 1980).

Consumable oral films for human or veterinary use are typically pliable water-soluble or water-swellable thin film dosage forms which may be rapidly dissolving or mucoadhesive and typically comprise a compound of formula I, a film-forming polymer, a binder, a solvent, a humectant, a plasticiser, a stabiliser or emulsifier, a viscosity-modifying agent and a solvent. Some components of the formulation may perform more than one function.

The compound of formula I may be water-soluble or insoluble. A water-soluble compound typically comprises from 1 weight % to 80 weight %, more typically from 20 weight % to 50 weight %, of the solutes. Less soluble compounds may comprise a greater proportion of the composition, typically up to

88 weight % of the solutes. Alternatively, the compound of formula I may be in the form of multiparticulate beads.

The film-forming polymer may be selected from natural polysaccharides, proteins, or synthetic hydrocolloids and is typically present in the range 0.01 to 99 weight %, more typically in the range 30 to 80 weight %.

Other possible ingredients include anti-oxidants, colorants, flavourings and flavour enhancers, preservatives, salivary stimulating agents, cooling agents, co-solvents (including oils), emollients, bulking agents, anti-foaming agents, surfactants and taste-masking agents.

Films in accordance with the invention are typically prepared by evaporative drying of thin aqueous films coated onto a peelable backing support or paper. This may be done in a drying oven or tunnel, typically a combined coater dryer, or by freeze-drying or vacuuming.

Solid formulations for oral administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

Suitable modified release formulations for the purposes of the invention are described in US Patent No. 6,106,864. Details of other suitable release technologies such as high energy dispersions and osmotic and coated particles are to be found in Pharmaceutical Technology On-line, 25(2), 1-14 by Verma *et al* (2001). The use of chewing gum to achieve controlled release is described in WO 00/35298.

The compounds of the invention may also be administered directly into the blood stream, into muscle, or into an internal organ. Suitable means for parenteral administration include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular, intrasynovial and subcutaneous. Suitable devices for parenteral administration include needle (including microneedle) injectors, needle-free injectors and infusion techniques.

Parenteral formulations are typically aqueous solutions which may contain excipients such as salts, carbohydrates and buffering agents (preferably to a pH of from 3 to 9), but, for some applications, they may be more suitably formulated as a sterile non-aqueous solution or as a dried form to be used in conjunction with a suitable vehicle such as sterile, pyrogen-free water.

The preparation of parenteral formulations under sterile conditions, for example, by lyophilisation, may readily be accomplished using standard pharmaceutical techniques well known to those skilled in the art.

The solubility of compounds of formula (I) used in the preparation of parenteral solutions may be increased by the use of appropriate formulation techniques, such as the incorporation of solubility-enhancing agents.

Formulations for parenteral administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release. Thus compounds of the invention may be formulated as a suspension or as a solid, semi-solid, or thixotropic liquid for administration as an implanted depot providing modified release of the active compound. Examples of such formulations include drug-coated stents and semi-solids and suspensions comprising drug-loaded poly(*dl*-lactic-coglycolic)acid (PGLA) microspheres.

The compounds of the invention may also be administered topically, (intra)dermally, or transdermally to the skin or mucosa. Typical formulations for this purpose include gels, hydrogels, lotions, solutions, creams, ointments, dusting powders, dressings, foams, films, skin patches, wafers, implants, sponges, fibres, bandages and microemulsions. Liposomes may also be used. Typical carriers include alcohol, water, mineral oil, liquid petrolatum, white petrolatum, glycerin, polyethylene glycol and propylene glycol. Penetration enhancers may be incorporated - see, for example, J Pharm Sci, 88 (10), 955-958 by Finnin and Morgan (October 1999).

Other means of topical administration include delivery by electroporation, iontophoresis, phonophoresis, sonophoresis and microneedle or needle-free (*e.g.* Powderject™, Bioject™, *etc.*) injection.

Formulations for topical administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

The compounds of the invention can also be administered intranasally or by inhalation, typically in the form of a dry powder (either alone, as a mixture, for example, in a dry blend with lactose, or as a mixed component particle, for example, mixed with phospholipids, such as phosphatidylcholine) from a dry powder inhaler or as an aerosol spray from a pressurised container, pump, spray, atomiser (preferably an atomiser using electrohydrodynamics to produce a fine mist), or nebuliser, with or without the use of a suitable propellant, such as 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane, or as nasal drops. For intranasal use, the powder may comprise a bioadhesive agent, for example, chitosan or cyclodextrin.

The pressurised container, pump, spray, atomizer, or nebuliser contains a solution or suspension of the compound(s) of the invention comprising, for example, ethanol, aqueous ethanol, or a suitable alternative agent for dispersing, solubilising, or extending release of the active, a propellant(s) as solvent and an optional surfactant, such as sorbitan trioleate, oleic acid, or an oligolactic acid.

Prior to use in a dry powder or suspension formulation, the drug product is micronised to a size suitable for delivery by inhalation (typically less than 5 microns). This may be achieved by any appropriate comminuting method, such as spiral jet milling, fluid bed jet milling, supercritical fluid processing to form nanoparticles, high pressure homogenisation, or spray drying.

Capsules (made, for example, from gelatin or hydroxypropylmethylcellulose, blisters and cartridges for use in an inhaler or insufflator may be formulated to contain a powder mix of the compound of the invention, a suitable powder base such as lactose or starch and a performance modifier such as *l*-leucine, mannitol, or magnesium stearate. The lactose may be anhydrous or in the form of the monohydrate, preferably the latter. Other suitable excipients include dextran, glucose, maltose, sorbitol, xylitol, fructose, sucrose and trehalose.

A suitable solution formulation for use in an atomiser using electrohydrodynamics to produce a fine mist may contain from 1µg to 20mg of the compound of the invention per actuation and the actuation volume may vary from 1µl to 100µl. A typical formulation may comprise a compound of formula (I), propylene glycol, sterile water, ethanol and sodium chloride. Alternative solvents which may be used instead of propylene glycol include glycerol and polyethylene glycol.

Suitable flavours, such as menthol and levomenthol, or sweeteners, such as saccharin or saccharin sodium, may be added to those formulations of the invention intended for inhaled/intranasal administration.

Formulations for inhaled/intranasal administration may be formulated to be immediate and/or modified release using, for example, PGLA. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

In the case of dry powder inhalers and aerosols, the dosage unit is determined by means of a valve which delivers a metered amount. Units in accordance with the invention are typically arranged to administer a metered dose or "puff" containing from 0.001 mg to 10 mg of the compound of formula (I). The overall daily dose will typically be in the range 0.001 mg to 40 mg which may be administered in a single dose or, more usually, as divided doses throughout the day.

The compounds of the invention may be administered rectally or vaginally, for example, in the form of a suppository, pessary, or enema. Cocoa butter is a traditional suppository base, but various alternatives may be used as appropriate.

Formulations for rectal/vaginal administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

The compounds of the invention may also be administered directly to the eye or ear, typically in the form of drops of a micronised suspension or solution in isotonic, pH-adjusted, sterile saline. Other formulations suitable for ocular and aural administration include ointments, gels, biodegradable (*e.g.* absorbable gel sponges, collagen) and non-biodegradable (*e.g.* silicone) implants, wafers, lenses and particulate or vesicular systems, such as niosomes or liposomes. A polymer such as crossed-linked

polyacrylic acid, polyvinylalcohol, hyaluronic acid, a cellulosic polymer, for example, hydroxypropylmethylcellulose, hydroxyethylcellulose, or methyl cellulose, or a heteropolysaccharide polymer, for example, gelan gum, may be incorporated together with a preservative, such as benzalkonium chloride. Such formulations may also be delivered by iontophoresis.

Formulations for ocular/aural administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted, or programmed release.

The compounds of the invention may be combined with soluble macromolecular entities, such as cyclodextrin and suitable derivatives thereof or polyethylene glycol-containing polymers, in order to improve their solubility, dissolution rate, taste-masking, bioavailability and/or stability for use in any of the aforementioned modes of administration.

Drug-cyclodextrin complexes, for example, are found to be generally useful for most dosage forms and administration routes. Both inclusion and non-inclusion complexes may be used. As an alternative to direct complexation with the drug, the cyclodextrin may be used as an auxiliary additive, *i.e.* as a carrier, diluent, or solubiliser. Most commonly used for these purposes are alpha-, beta- and gamma-cyclodextrins, examples of which may be found in International Patent Applications Nos. WO 91/11172, WO 94/02518 and WO 98/55148.

Inasmuch as it may desirable to administer a combination of active compounds, for example, for the purpose of treating a particular disease or condition, it is within the scope of the present invention that two or more pharmaceutical compositions, at least one of which contains a compound in accordance with the invention, may conveniently be combined in the form of a kit suitable for coadministration of the compositions.

Thus the kit of the invention comprises two or more separate pharmaceutical compositions, at least one of which contains a compound of formula (I) in accordance with the invention, and means for separately retaining said compositions, such as a container, divided bottle, or divided foil packet. An example of such a kit is the familiar blister pack used for the packaging of tablets, capsules and the like.

The kit of the invention is particularly suitable for administering different dosage forms, for example, oral and parenteral, for administering the separate compositions at different dosage intervals, or for titrating the separate compositions against one another. To assist compliance, the kit typically comprises directions for administration and may be provided with a so-called memory aid.

Other aspects of the invention are enumerated in the claims.

Biological Data

Example number	MC4 EC50 (nM)	MC4 MSH Ki (nM)	MC3 EC50 (nM)	MC3 MSH Ki (nM)	MC4 AgRP Ki (nM)	HLM (µL/min/ mg)	RLM (µL/min/ mg)	% Inhibition of 3A4 metabolism at 3 uM
1	<0.52		43.9		39	<7.0	<8.5	54
2	4.53	27	4.26	124	59	<12.0	31	64
3	11.9		16.4			<7.0	<19.8	60
4			55.9		51	60	74	38
5	137		203		552	<7.0	27	34
6	18.9		1460		456		<8.5	32
7	40		1600		714	21	11	19
8	27.5		1090		643	>440	>510	94
9	39.3		520		523	240	411	68
10	11.9	276	493	977	223	20.5	42	19
11	111				417	14		
12	91.6					>352	88.5	
13	37.6		1020		106			6
14	115		129			<9.0	<9.75	
15	53.9		>3340 0					
16	34.3		323		251	<45.5	<8.5	83
17	1.59	112	54.9	332	20	>440	>510	35
18	55.5		>8520		965	67	68	34
19	6.5	85.4	425	568	79	21	21	50
20	16.4	251	1120	1020	253	31	51.5	35
21	2.81		283		66	144	58.5	25
22	19.8		1050	5560	5960	179	96	54
23	4.75	65.7	185	264	79	<15.5	<8.5	35
24	59.3		2510		>955	355	>510	87
25	12.4	10.9	189	<0.105	278	308	172	16
26	22.5		4210		363	70	>510	61
27	4.54		390		100	51	31	64
28	24.4		938	1670	516	33	51	77
29	7.54				40	105	36	59
30	5.77		61.5		112	141	69.5	38
31	22.9		410		526	188	292	60
32	8.78	150	76.6	456	160	8	<8.5	31
33	13.4		193		220	186	72	19
34	39.2				375	<7.0	<8.5	50
35	62.2		878		386	100	92	46
36	168				1020	<7.0	17	59
37			325		422	19.5	23	45
38	102				336	<7.0	<8.5	58
39			2100		751	95	58	30
40	69.8		580		430	<7.0	<8.5	64
41	655		>3330 0		3750	21	30	52
42			>2030 0		888	25	25	59
43	49.3		1590		248	37		44

44	284		>9630		2130			27
45	44.4		66.1		251	<7.0	<8.5	69
46	15		50.8	551	134	<7.0	<8.5	74

The effects of the compound of Example 2 at 3mg/kg and 10mg/kg on cumulative food intake over 24 hours, and body weight change over 24 hours, compared to vehicle, are expressed in Figures 1 and 2.

The invention is illustrated by the following non-limiting examples in which the following abbreviations and definitions are used:

APCI	atmospheric pressure chemical ionisation mass spectrum
$[\alpha]_D$	specific rotation at 589 nm.
br	broad
Celite®	filter agent
δ	chemical shift
d	doublet
dd	double doublet
EI	electrospray ionisation
Ex	example
LRMS	low resolution mass spectrum
m	multiplet
m/z	mass spectrum peak
NMR	nuclear magnetic resonance
Prec	precursor
Prep	preparation
psi	pounds per square inch
q	quartet
s	singlet
t	triplet
tlc	thin layer chromatography

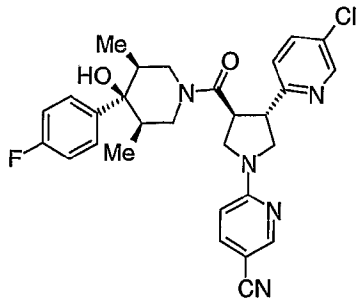
For synthetic convenience whilst in many instances compounds have been initially isolated in their free-base form, these have often been converted to their corresponding hydrochloride salts for analytical identification purposes. For the avoidance of doubt, both the free-base and HCl salt forms are considered provided herein.

For the avoidance of doubt, named compounds used herein have been named using ACD Labs Name Software v7.11™.

EXAMPLES

Example 1

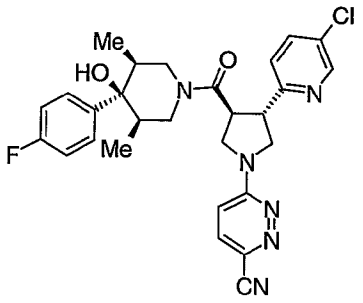
6-[(3S,4S)-3-(5-Chloropyridin-2-yl)-4-{[(3R,4R,5S)-4-(4-fluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]nicotinonitrile



2-Chloro-5-cyanopyridine (96 mg, 0.69 mmol) was added to a solution of the pyrrolidine from preparation 10 (200 mg, 0.46 mmol) and N-ethyldiisopropylamine (0.32 mL, 1.8 mmol) in acetonitrile (10 mL) and the mixture was heated at 70°C under nitrogen overnight. The solvent was removed *in vacuo* and the residue was purified by column chromatography (silica) eluting with dichloromethane, increasing polarity to 5% methanol in dichloromethane, to give the title compound (191 mg, 77%) as a white solid. ^{1}H NMR (CD_3OD, 400 MHz) δ 0.4-0.6 (6H, 4 x d), 0.78-0.82, 1.60-1.68 and 1.97-2.05 (2H, 3 x m), 2.73-2.80 (1H, m), 3.00-3.20 (1H, m), 3.68-4.37 (8H, m), 6.62 (1H, m), 7.01-7.08 and 7.37-7.48 (5H, 2 x m), 7.74 (1H, m), 7.80 and 7.95 (1H, 2 x dd), 8.40 (1H, m), 8.57 and 8.60 (1H, 2 x d); LRMS (EI^+) 534 [MH^+]; $[\alpha]_D^{25}$ = -47.0 (*c* = 0.215, MeOH).

Example 2

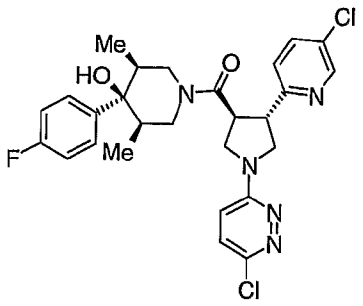
6-[(3S,4S)-3-(5-Chloropyridin-2-yl)-4-{[(3R,4R,5S)-4-(4-fluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]pyridazine-3-carbonitrile



3-Chloro-6-cyanopyridazine (prepared according to US 3,637,691) (20 mg, 0.14 mmol) was added to a solution of the pyrrolidine from preparation 10 (40 mg, 0.09 mmol) and N-ethyldiisopropylamine (0.06 mL, 0.37 mmol) in acetonitrile (10 mL) and the mixture was heated at 70°C under nitrogen overnight. The solvent was removed *in vacuo* and the residue was purified by column chromatography (silica) eluting with dichloromethane, increasing polarity to 5% methanol in dichloromethane, to give the title compound (41 mg, 83%) as a white solid. ^{1}H NMR (CD_3OD, 400 MHz) δ 0.4-0.6 (6H, 4 x d), 0.78-0.85, 1.60-1.69 and 1.97-2.10 (2H, 3 x m), 2.72-2.80 (1H, m), 3.00-3.23 (1H, m), 3.68-4.38 (8H, m), 6.99-7.08 and 7.38-7.50 (6H, 2 x m), 7.70 (1H, d), 7.80 and 7.94 (1H, 2 x dd), 8.58 and 8.61 (1H, 2 x d); LRMS (EI^+) 535 [MH^+].

Example 3

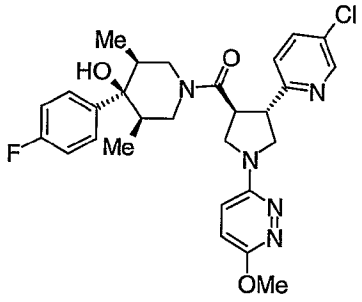
(3R,4R,5S)-1-{[(3S,4S)-1-(6-Chloropyridazin-3-yl)-4-(5-chloropyridin-2-yl)pyrrolidin-3-yl]carbonyl}-4-(4-fluorophenyl)-3,5-dimethylpiperidin-4-ol



1,6-Dichloropyridazine (173 mg, 1.2 mmol) was added to a solution of the pyrrolidine from preparation 10 (100 mg, 0.23 mmol) and N-ethyldiisopropylamine (0.16 mL, 0.93 mmol) in acetonitrile (5 mL) and the mixture was heated at 70°C under nitrogen overnight. The solvent was removed *in vacuo* and the residue was purified by column chromatography (silica) eluting with dichloromethane, increasing polarity to 5% methanol in dichloromethane, to give the title compound (52 mg, 42%) as a white solid. ^{1}H NMR (CD_3OD, 400 MHz) δ 0.4-0.6 (6H, 4 x d), 0.78-0.85, 1.60-1.69 and 1.97-2.10 (2H, 3 x m), 2.72-2.80 (1H, m), 3.00-3.23 (1H, m), 3.68-4.38 (8H, m), 6.99-7.08 and 7.38-7.50 (6H, 2 x m), 7.70 (1H, d), 7.80 and 7.94 (1H, 2 x dd), 8.58 and 8.61 (1H, 2 x d); LRMS (EI^+) 544 [MH^+].

Example 4

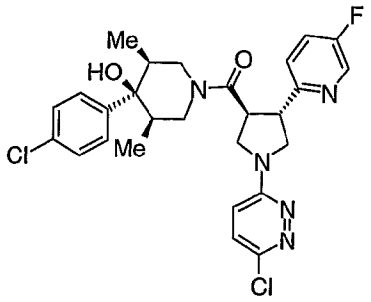
(3R,4R,5S)-1-{[(3S,4S)-4-(5-chloropyridin-2-yl)-1-(6-methoxypyridazin-3-yl)pyrrolidin-3-yl]carbonyl}-4-(4-fluorophenyl)-3,5-dimethylpiperidin-4-ol



Sodium t-butoxide (31 mg, 0.32 mmol), 3-chloro-6-methoxypyridazine (34 mg, 0.23 mmol), tris(dibenzylideneacetone)dipalladium (0) (8.5 mg, 0.009 mmol) and 2,2'-bis(diphenylphosphino)-1,1'-binaphthalene (11.5 mg, 0.0185 mmol) were added to a solution of the pyrrolidine from preparation 10 (100 mg, 0.23 mmol) in toluene (10 mL) and the mixture was heated at 80°C under nitrogen overnight. The solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (25 mL), washed with water, dried (MgSO4) and evaporated. Purification by column chromatography (silica) eluting with dichloromethane, increasing polarity to 5% methanol in dichloromethane, gave the title compound (48 mg, 40%) as a yellow foam. ^{1}H NMR (CD_3OD, 400 MHz) δ 0.4-0.62 (d+t+t, 6H), 0.86 (m, 1H), 1.65 (m, 1H), 1.93-2.08 (br, 1H), 2.75 (m, 1H), 3.17 (t, 1H), 3.74 (m, 3H), 3.95 (s, 3H), 3.96-4.21 (m, 3H), 4.32 (d, 1H), 6.98-7.1 (m, 5H), 7.38-7.48 (m, 2H), 7.79+7.48 (2 x dd, 1H), 8.56 (d, 1H); LRMS (EI^+) 540 [MH^+].

Example 5

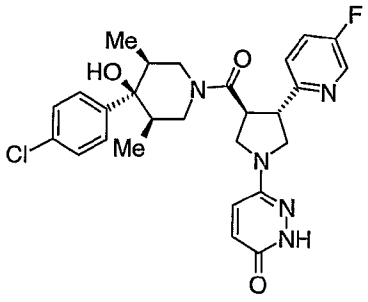
(3R,4R,5S)-4-(4-chlorophenyl)-1-{[(3S,4S)-1-(6-chloropyridazin-3-yl)-4-(5-fluoropyridin-2-yl)pyrrolidin-3-yl]carbonyl}-3,5-dimethylpiperidin-4-ol



To a solution of (3R,4R,5S)-4-(4-chlorophenyl)-1-{[(3S,4S)-4-(5-fluoropyridin-2-yl)pyrrolidin-3-yl]carbonyl}-3,5-dimethylpiperidin-4-ol (prepared by the same methods as used for the amine of preparation 10, starting from the aldehyde of preparation 17 and (3R,4s,5S)-4-(4-chlorophenyl)-3,5-dimethylpiperidin-4-ol, prepared according to international patent application publication number WO 2005/077935) (120 mg, 0.28 mmol) in dimethyl sulfoxide (2 mL) was added 3,6-dichloropyridazine (98 mg, 0.56 mmol), triethylamine (0.12 mL, 0.84 mmol), and caesium fluoride (13 mg, 0.084 mmol). The mixture was stirred at 110°C under nitrogen for 3 hours. The reaction mixture was diluted with methanol (5 mL) and loaded onto an SCX column, eluting with methanol to remove non basic material and dimethylsulfoxide, followed by 2M NH_3 in methanol to elute the basic product. The solvent was removed *in vacuo* to yield the title compound (74 mg, 49%) as a colourless gum. ^{1}H NMR (CD_3OD, 400 MHz) δ 0.44-0.60 (6H, 4 x d), 0.95-1.02, 1.64-1.73 and 1.94-2.09 (2H, 3 x m), 2.69-2.79 (1H, m), 2.99-3.06 and 3.16-3.22 (1H, 2 x m), 3.74-3.79 (3H, m), 4.01-4.24 (4H, m), 4.32-4.36 (1H, m), 7.02-7.07 (1H, m), 7.29-7.70 (7H, m), 8.45-8.49 (1H, m); LRMS (EI+) 544 [MH+].

Example 6

6-[(3S,4S)-3-{[(3R,4R,5S)-4-(4-chlorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}-4-(5-fluoropyridin-2-yl)pyrrolidin-1-yl]pyridazin-3(2H)-one

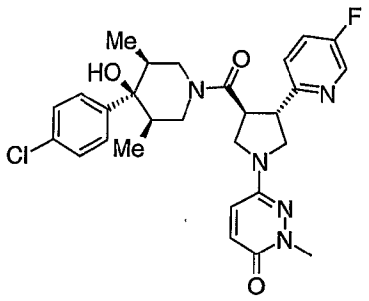


A solution of chloropyridazine from Example 5 (70 mg, 0.13 mmol) was dissolved in degassed acetic acid and stirred at reflux under nitrogen overnight. The solvent was removed *in vacuo* and the residue was purified by column chromatography (silica) eluting with dichloromethane/methanol/aq. ammonia 95/5/0.5. This yielded the title compound as an off-white solid (37 mg, 55%). ^{1}H NMR (CD_3OD, 400 MHz) δ 0.43-0.59 (6H, 4 x d), 0.94-1.03, 1.64-1.73 and 1.93-2.03 (2H, 3 x m), 2.65-2.78 (1H, m), 2.97-3.03 and

3.14-3.20 (1H, 2 x m), 3.62-3.79 (3H, m), 3.86-4.17 (4H, m), 4.31-4.35 (1H, m), 6.88-6.91 (1H, m), 7.30-7.42 (5H, m), 7.47-7.57 (1H, m), 7.63-7.68 (1H, m), 8.44-8.48 (1H, m); LRMS (EI+) 526 [MH+].

Example 7

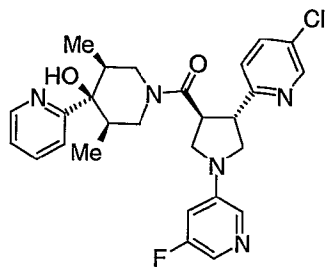
6-[(3S,4S)-3-{[(3R,4R,5S)-4-(4-chlorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}-4-(5-fluoropyridin-2-yl)pyrrolidin-1-yl]-2-methylpyridazin-3(2H)-one



To a solution of the pyridazinone from Example 6 (30 mg, 0.057 mmol) in dimethylformamide (2 mL) was added sodium hexamethydisilazide 1M in tetrahydrofuran (0.07 mL, 0.07 mmol) and lithium bromide (6 mg, 0.07 mmol). The mixture was stirred at room temperature under nitrogen for 30 minutes then methyl iodide (0.004 mL, 0.07 mmol) was added and the mixture was stirred under nitrogen at room temperature for 2 hours. The solvent was removed *in vacuo* and the residue was purified by column chromatography (silica) eluting with dichloromethane/methanol/aq. ammonia 95/5/0.5. This yielded the title compound as a yellow solid. ^{1}H NMR (CD_3OD, 400 MHz) δ 0.44-0.59 (6H, 4 x d), 0.94-1.03, 1.64-1.73 and 1.95-2.04 (2H, 3 x m), 2.68-2.78 (1H, m), 2.95-3.01 and 3.14-3.21 (1H, 2 x m), 3.62-3.81 (6H, m), 3.87-4.17 (4H, m), 4.31-4.35 (1H, m), 6.87-6.90 (1H, m), 7.25-7.34 (4H, m), 7.38-7.42 (1H, m), 7.48-7.58 (1H, m), 7.64-7.69 (1H, m), 8.44-8.48 (1H, m); LRMS (EI+) 540 [MH+].

Example 8

(3R,4R,5S)-1-{[(3S,4S)-4-(5-chloropyridin-2-yl)-1-(5-fluoropyridin-3-yl)pyrrolidin-3-yl]carbonyl}-3,5-dimethyl-4-pyridin-2-ylpiperidin-4-ol

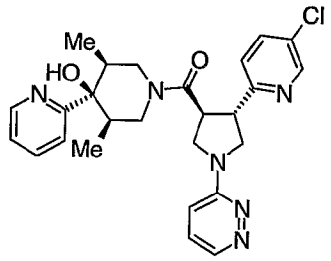


To a solution of (3R,4R,5S)-1-{[(3S,4S)-4-(5-chloropyridin-2-yl)pyrrolidin-3-yl]carbonyl}-3,5-dimethyl-4-pyridin-2-ylpiperidin-4-ol (prepared by the same method as used for the amine of preparation 10, starting from (3R,4s,5S)-3,5-dimethyl-4-pyridin-2-ylpiperidin-4-ol, prepared according to international patent application publication number WO 2005/077935) (50 mg, 0.12 mmol) in toluene (5 mL), was added 3-bromo, 5-fluoropyridine (25 mg, 0.14 mmol), tris(dibenzylidineacetone)dipalladium (4.4 mg, 0.0048 mmol), BINAP (6 mg, 0.0096 mmol) and sodium tert-butoxide (26 mg, 0.27 mmol). The mixture was stirred at 80°C under nitrogen overnight. The solvent was removed *in vacuo* and the residue was purified

by column chromatography (silica) eluting with dichloromethane/methanol/aq. ammonia 99/1/0.1, increasing polarity to 95/5/0.5. This gave the title compound (11 mg, 18%) as a yellow gum. ^{1}H NMR (CD_3OD, 400 MHz) δ 0.33-0.53 (6H, 4 x d), 0.81-0.93, 1.81-1.92 and 2.08-2.28 (2H, 3 x m), 2.69-2.78 (1H, m), 2.99-3.20 (1H, m), 3.61-3.94 (5H, m), 4.01-4.23 (2H, m), 4.34-4.42 (1H, m), 6.81-6.90 (1H, m), 7.26-7.50 (3H, m), 7.70-7.94 (4H, m), 8.51-8.62 (2H, m); LRMS (EI+) 510 [MH+].

Example 9

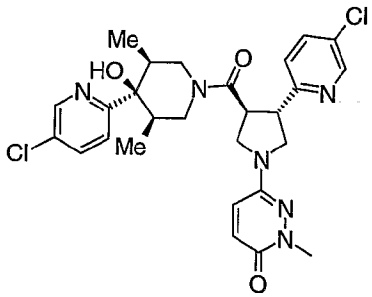
(3R,4R,5S)-1-{[(3S,4S)-4-(5-chloropyridin-2-yl)-1-pyridazin-3-ylpyrrolidin-3-yl]carbonyl}-3,5-dimethyl-4-pyridin-2-ylpiperidin-4-ol



To a solution of (3R,4R,5S)-1-{[(3S,4S)-4-(5-chloropyridin-2-yl)pyrrolidin-3-yl]carbonyl}-3,5-dimethyl-4-pyridin-2-ylpiperidin-4-ol (prepared by the same method as used for the amine of preparation 10, starting from (3R,4s,5S)-3,5-dimethyl-4-pyridin-2-ylpiperidin-4-ol, prepared according to international patent application publication number WO 2005/077935) (50 mg, 0.12 mmol) in DMSO (2 mL) was added 3-chloropyridazine (28 mg, 0.24 mmol), caesium fluoride (18 mg, 0.12 mmol) and triethylamine (0.05 mL, 0.36 mmol). The mixture was stirred at 100°C under nitrogen overnight. The reaction mixture was diluted with 10 mL ethyl acetate and washed with 3 x 20 mL of water. The combined aqueous extracts were extracted with 10 mL ethyl acetate and the combined organic extracts were washed with 10 mL brine, dried ($MgSO_4$) and the solvent was removed *in vacuo*. The residue was purified by column chromatography (silica) eluting with dichloromethane/methanol/aq. ammonia 99/1/0.1, increasing polarity to 95/5/0.5. This gave the title compound (16 mg, 27%) as a yellow gum. ^{1}H NMR (CD_3OD, 400 MHz) δ 0.20-0.37 (6H, 4 x d), 0.91-1.13, 1.67-1.76 and 1.94-2.09 (2H, 3 x m), 2.54-2.62 (1H, m), 2.87-2.93 and 2.99-3.05 (1H, 2 x m), 3.61-3.74 (3H, m), 3.86-4.08 (4H, m), 4.20-4.26 (1H, m), 6.83-6.88 (1H, m), 7.11-7.44 (4H, m), 7.63-7.78 (2H, m), 8.30-8.46 (3H, m); LRMS (EI+) 493 [MH+].

Example 10

6-[(3S,4S)-3-(5-chloropyridin-2-yl)-4-{[(3R,4R,5S)-4-(5-chloropyridin-2-yl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]-2-methylpyridazin-3(2H)-one



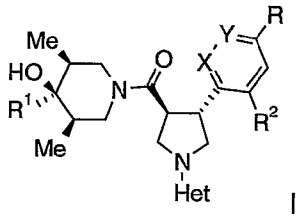
To a solution of the carboxylic acid from preparation 15 (42 mg, 0.08 mmol) in dichloromethane (3 mL) was added N-ethyldiisopropylamine (0.04 mL, 0.25 mmol), 1-hydroxybenzotriazole (15 mg, 0.095 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide and the mixture was stirred under nitrogen for 30 minutes. The amine from preparation 16 was added and the mixture was stirred under nitrogen overnight. The reaction mixture was diluted with dichloromethane (20 mL) and washed with saturated $NaHCO_3$ (20 mL) and brine (20 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to give a yellow oily solid. This was purified by column chromatography (silica), eluting with dichloromethane and increasing the polarity to 95/5 dichloromethane/methanol to yield the title compound as yellow solid (31 mg, 67%). ^1H NMR (CD_3OD, 400 MHz) δ 0.36-0.6 (m, 6H), 1.18 (br, 1H), 1.89 (br, 1H), 2.16 (br, 1H), 2.71 (m, 1H), 3.13 (m, 1H), 3.6-4.2 (s + m, 9H), 4.33 (d, 1H), 6.89 (d, 1H), 7.2-7.5 (m, 3H), 7.78-7.92 (m, 2H), 8.56 (d, 2H); LRMS (EI^+) 558 [MH^+].

Examples 11-46

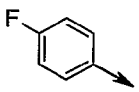
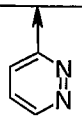
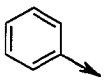
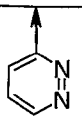
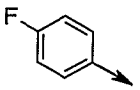
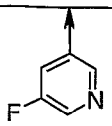
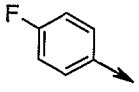
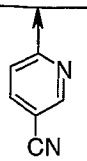
Examples 11-46 were prepared according to the methods described above for examples 1-10, starting from the appropriate pyridine aldehyde[1] and the appropriate 4 substituted 3,5-dimethylpiperidin-4-ol.[2]

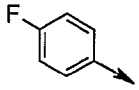
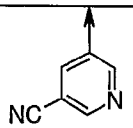
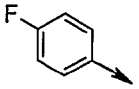
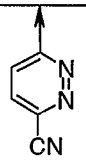
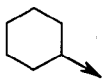
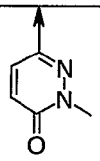
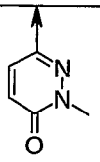
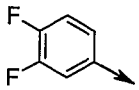
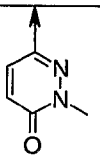
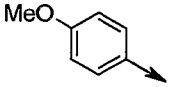
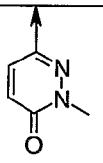
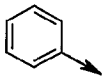
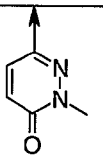
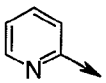
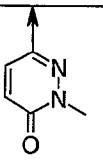
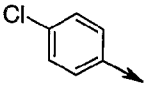
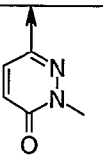
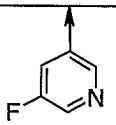
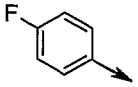
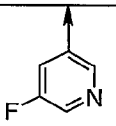
1. 2-Methoxypyridine-5-carbaldehyde is commercially available. Other aldehydes are described in preparations 2, 17, 18 and 22.

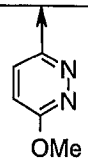
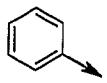
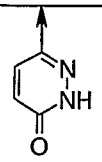
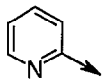
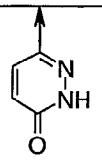
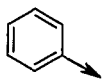
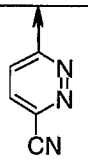
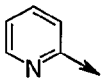
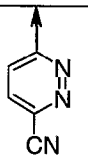
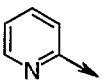
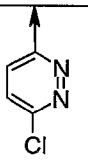
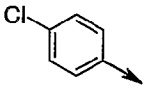
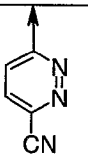
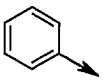
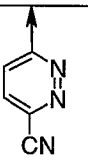
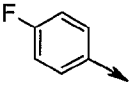
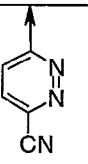
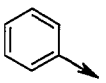
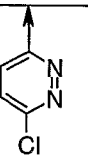
2. (3R,4s,5S)-4-(5-Chloropyridin-2-yl)-3,5-dimethylpiperidin-4-ol is described in preparation 16. The syntheses of the other required piperidinols are described in international patent application publication number WO 2005/077935.

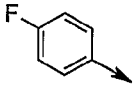
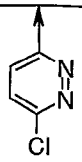
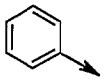
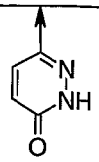
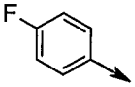
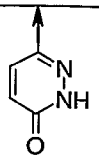
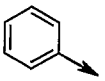
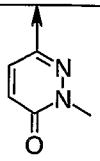
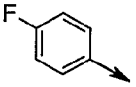
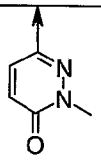
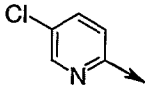
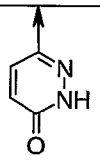
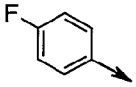
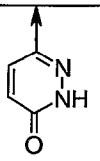
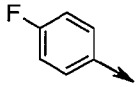
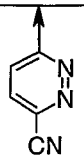
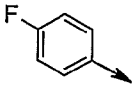
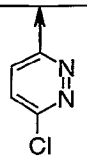
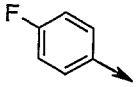
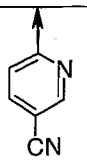


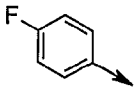
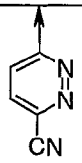
I

Example	X	Y	R	R^1	R^2	Het	Data
11	CH	N	-OMe		H		LRMS (APCI+) 506 [MH+]
12	CH	N	-OMe		H		LRMS (EI+) 488 [MH+]
13	CH	N	-OMe		H		LRMS (EI+) 523 [MH+]
14	CH	N	-OMe		H		LRMS (EI+) 530 [MH+]

15	CH	N	-OMe		H		LRMS (EI+) 530 [MH+]
16	CH	N	-OMe		H		LRMS (APCI+) 531 [MH+]
17	N	CH	Cl		H		LRMS (APCI+) 528 [MH+]
18	N	CH	Cl		H		LRMS (APCI+) 486 [MH+]
19	N	CH	Cl		H		LRMS (APCI+) 558 [MH+]
20	N	CH	Cl		H		LRMS (APCI+) 552 [MH+]
21	N	CH	Cl		H		LRMS (APCI+) 522 [MH+]
22	N	CH	Cl		H		LRMS (EI+) 523 [MH+]
23	N	CH	Cl		H		LRMS (APCI+) 556 [MH+]
24	N	CH	Cl		H		LRMS (APCI+) 473 [MH+]
25	N	CH	Cl		H		LRMS (APCI+) 527 [MH+]

26	N	CH	Cl		H		LRMS (APCI+) 486 [MH+]
27	N	CH	Cl		H		LRMS (APCI+) 508 [MH+]
28	N	CH	Cl		H		LRMS (EI+) 509 [MH+]
29	N	CH	Cl		H		LRMS (APCI+) 517 [MH+]
30	N	CH	Cl		H		LRMS (EI+) 518 [MH+]
31	N	CH	Cl		H		LRMS (EI+) 527 [MH+]
32	N	CH	F		H		LRMS (EI+) 535 [MH+]
33	N	CH	F		H		LRMS (EI+) 501 [MH+]
34	N	CH	F		H		LRMS (EI+) 519 [MH+]
35	N	CH	F		H		LRMS (EI+) 510 [MH+]

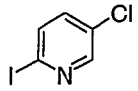
36	N	CH	F		H		LRMS (EI+) 528 [MH+]
37	N	CH	F		H		LRMS (EI+) 492 [MH+]
38	N	CH	F		H		LRMS (EI+) 510 [MH+]
39	N	CH	F		H		LRMS (EI+) 506 [MH+]
40	N	CH	F		H		LRMS (EI+) 524 [MH+]
41	N	CH	-OMe		H		LRMS (EI^+) 539 [MH^+]
42	N	CH	-OMe		H		LRMS ($APCI^+$) 522 [MH^+]
43	N	CH	-OMe		H		LRMS ($APCI^+$) 531 [MH^+]
44	N	CH	-OMe		H		LRMS ($APCI^+$) 540 [MH^+]
45	N	CH	-CN		H		LRMS (APCI+) 525 [MH+]

46	N	CH	-CN		H		LRMS (APCI+) 526 [MH+]

PREPARATIONS

Preparation 1

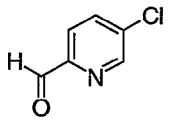
5-Chloro-2-iodopyridine



Acetyl chloride (11.05 mL, 0.155 mol) was added to a solution of 2-bromo-5-chloropyridine (20.0 g, 0.103 mol) in acetonitrile (120 mL) followed by sodium iodide (23.3 g, 0.155 mol) and the mixture was heated at reflux with a drying tube fitted for 3 hours. The reaction was cooled in an ice bath, carefully basified with saturated aqueous potassium carbonate then extracted with ethyl acetate (2 x 100 mL). The combined organic layers were washed with saturated aqueous sodium sulfite (200 mL), dried ($MgSO_4$) and evaporated. The residue was then re-submitted to identical reaction and work-up conditions in order to ensure complete reaction and this gave the title compound (18.71 g, 75%) as a brown solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.30 (1H, dd), 7.65 (1H, d), 8.35 (1H, d); LRMS ($APCI^+$) 240 [MH^+].

Preparation 2

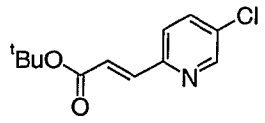
5-Chloropyridine-2-carbaldehyde



The iodide from preparation 2 (18.71 g, 78.1 mmol) was dissolved in tetrahydrofuran (100 mL) and cooled to −15°C under nitrogen. A solution of isopropyl magnesium chloride in tetrahydrofuran (2M, 42.2 mL, 84.4 mmol) was then added dropwise, ensuring that the temperature stayed below 0°C. The reaction mixture was cooled to −15°C, stirred for 1 hour and dimethylformamide (9.0 mL, 116 mmol) was added dropwise, maintaining the temperature below 0°C. The reaction mixture was allowed to warm to room temperature and stirred for 1 hour before being re-cooled to 0°C and carefully quenched by the dropwise addition of 2M HCl (100 mL). After the addition was complete the mixture was stirred at room temperature for 30 min before the pH was adjusted to 6-7 by the addition of saturated aqueous sodium hydrogen carbonate. The organic layer was separated and the aqueous layer was extracted with dichloromethane (2 x 200 mL). The combined organic layers were washed with water (200 mL), dried ($MgSO_4$) and concentrated on a rotary evaporator, keeping the temperature below 30°C, to give crude product (13.7 g) as a brown oil which was used without further purification. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35 (1H, d), 7.95 (1H, d), 8.73 (1H, s), 10.02 (1H, s); LRMS ($APCI^+$) 142 [MH^+].

Preparation 3

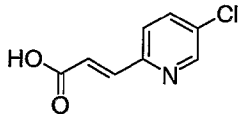
tert-Butyl (2E)-3-(5-chloropyridin-2-yl)acrylate



n-Butyl lithium (2.5 M in hexanes, 34 mL, 85 mmol) was added dropwise to a solution of tert-butyl diethylphosphonoacetate (19.1 mL, 81 mmol) in diethyl ether (80 mL) at −78°C under nitrogen and stirring was continued for 30 min. A solution of the crude aldehyde from preparation 2 (from 78.1 mmol of the iodide of preparation 1) in diethyl ether (20 mL) was then added dropwise, keeping the temperature below −65°C. Once the addition was complete the mixture was allowed to warm to room temperature over 2 hours before being cautiously quenched by the addition of saturated aqueous ammonium chloride (200 mL). The mixture was extracted with diethyl ether (2 x 150 mL) and the combined organic extracts were washed with brine (200 mL), dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography (silica), eluting with pentane increasing polarity to pentane/ethyl acetate 8:2, to give the title compound (13.34 g, 74% over 2 steps) as an oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.51, (9H, s), 6.79 (1H, d), 7.35 (1H, d), 7.52, (1H, d), 7.66 (1H, dd), 8.55 (1H, d); LRMS (APCI$^+$) 240 [MH$^+$].

Preparation 4

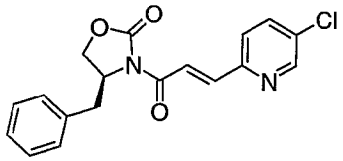
(2E)-3-(5-Chloropyridin-2-yl)acrylic acid trifluoroacetic acid salt



A solution of trifluoroacetic acid (10 mL) in dichloromethane (10 mL) was added dropwise to an ice cooled solution of the ester from preparation 3 (2.09 g, 8.7 mmol) in dichloromethane (10 mL) and the resulting mixture was stirred at room temperature overnight. The solvent was removed *in vacuo*, toluene (10 mL) was added and removed in vacuo and dichloromethane (10 mL) was added and removed *in vacuo* to give the title compound (2.44 g, 94%) as a red solid. ^{1}H NMR (CD_3OD, 400 MHz) δ 6.86 (1H, d), 7.64 (2H, m), 7.87 (1H, dd), 8.59 (1H, d); LRMS (APCI$^+$) 184 [MH$^+$].

Preparation 5

(4S)-4-Benzyl-3-[(2E)-3-(5-chloropyridin-2-yl)prop-2-enoyl]-1,3-oxazolidin-2-one

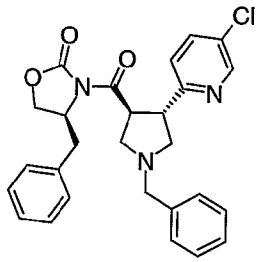


A solution of the acid from preparation 4 (2.44 g, 8.2 mmol) in tetrahydrofuran (15 mL) was cooled to -78°C under nitrogen. Triethylamine (2.85 mL, 20 mmol) was added dropwise followed by trimethylacetyl chloride (1.11 mL, 9.0 mmol), controlling the rate of addition so that the temperature stayed below -65°C. The mixture was then stirred at −78°C for 2 hours. ^{n}BuLi (2.5 M in hexanes, 4.26 mL, 10.7 mmol) was added dropwise to a solution of (4S)-4-benzyl-1,3-oxazolidin-2-one (1.74 g, 9.8 mmol) in tetrahydrofuran (15 mL) under nitrogen at −78°C, controlling the rate of addition so that the temperature stayed below −65°C. After stirring at −78°C for 20 minutes the solution of oxazolidinone anion was added via cannula

to the mixed anhydride solution at −78°C. The reaction mixture was stirred at −78°C for 20 minutes then allowed to warm slowly to room temperature overnight. The reaction was quenched by the addition of saturated aqueous ammonium chloride solution (30 mL) and then concentrated *in vacuo* to remove the tetrahydrofuran. The solid precipitate was filtered and washed with diethyl ether to give the title compound (1.52 g, 54%) as a buff solid. The ether washings were evaporated to dryness, slurried in diethyl ether and filtered to give further product (0.42 g, 15%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.84 (1H, t), 3.37 (1H, d), 4.22 (2H, m), 4.78 (1H, m), 7.2-7.4 (5H, m), 7.51 (1H, d), 7.69 (1H, d), 7.86 (1H, d), 8.23 (1H, d), 8.62 (1H, s); LRMS (APCI$^+$) 343 [MH$^+$].

Preparation 6

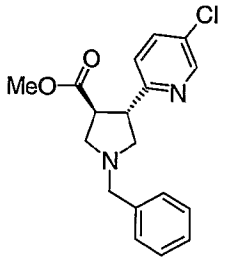
(4S)-4-Benzyl-3-{[(3S,4S)-1-benzyl-4-(5-chloropyridin-2-yl)pyrrolidin-3-yl]carbonyl}-1,3-oxazolidin-2-one



Trifluoroacetic acid (90 μL, 1.2 mmol) was added to a suspension of the oxazolidinone from preparation 5 (1.93 g, 5.6 mmol) in dichloromethane (20 mL) and *N*-benzyl-*N*-(methoxymethyl)trimethylsilylamine (2.3 mL, 9.0 mmol) was then added dropwise over 10 minutes. After the addition was complete the reaction was allowed to stir at room temperature overnight. The reaction mixture was treated with saturated aqueous sodium hydrogen carbonate solution (20 mL) and the layers were separated. The aqueous layer was extracted with dichloromethane (2 x 20 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography (silica), eluting with ethyl acetate/pentane 2:8, increasing polarity to 2:3 to give the undesired (4S)-4-benzyl-3-{[(3R,4R)-1-benzyl-4-(5-chloropyridin-2-yl)pyrrolidin-3-yl]carbonyl}-1,3-oxazolidin-2-one (1.16 g, 44%) as the first eluting component and the desired (4S)-4-benzyl-3-{[(3S,4S)-1-benzyl-4-(5-chloropyridin-2-yl)pyrrolidin-3-yl]carbonyl}-1,3-oxazolidin-2-one (1.18 g, 45%) as the second eluting component. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.75 (2H, m), 2.92 (1H, m), 3.20 (3H, m), 3.27 (1H, br), 3.68 (2H, br), 4.14 (2H, m), 4.23 (1H, m), 4.50 (1H, m), 4.67 (1H, m), 7.10-7.40 (11H, m), 7.58 (1H, dd), 8.50 (1H, d); LRMS (APCI$^+$) 476 [MH$^+$].

Preparation 7

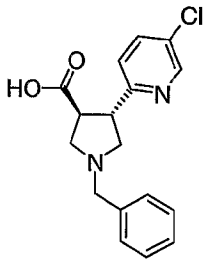
Methyl (3S,4S)-1-benzyl-4-(5-chloropyridin-2-yl)pyrrolidine-3-carboxylate



Sodium methoxide (664 mg, 12 mmol) was added to a solution of the oxazolidinone from preparation 6 (1.17 g, 2.5 mmol) and dimethyl carbonate (1.03 mL, 12 mmol) in dichloromethane (15 mL) and the reaction was stirred at room temperature overnight. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between ethyl acetate (50 mL) and water (30 mL). The aqueous layer was neutralised by the addition of 2M HCl (~ 6 mL) and then concentrated *in vacuo*. The residue was triturated with acetonitrile (25 mL) and then filtered. Concentration of the filtrate gave (3S,4S)-1-benzyl-4-(5-chloropyridin-2-yl)pyrrolidine-3-carboxylic acid (123 mg, 16%) as yellow solid (see preparation 8 for spectroscopic data). The ethyl acetate layer was dried ($MgSO_4$) and evaporated. Purification of the residue by column chromatography (silica), eluting with ethyl acetate/pentane 2:8, increasing polarity to 2:3 gave the title compound (371 mg, 45%) as a colourless oil. ^1H NMR ($CDCl_3$, 400 MHz) δ 2.71 (1H, t), 2.97 (1H, t), 3.05 (2H, m), 3.23 (1H, m), 3.63 (5H, m), 3.82 (1H, q), 7.15-7.35 (6H, m), 7.55 (1H, d), 8.46 (1H, s); LRMS ($APCI^+$) 331 [MH^+].

Preparation 8

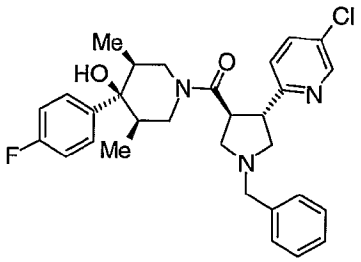
(3S,4S)-1-Benzyl-4-(5-chloropyridin-2-yl)pyrrolidine-3-carboxylic acid bis hydrochloride



A solution of NaOH (135 mg, 3.3 mmol) in water (5 mL) was added to a solution of the ester from preparation 7 (371 mg, 1.1 mmol) in dioxane (10 mL) and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated *in vacuo*, taken up in water (10 mL) and neutralised with 2M HCl (~1.7 mL). The mixture was then concentrated *in vacuo*, triturated with acetonitrile (20 mL) and filtered. The filtrate was acidified with 2M ethereal HCl and concentrated in vacuo to give the title compound (290 mg, 68%) as a solid. ^1H NMR (CD_3OD, 400 MHz) δ 3.40-4.20 (6H, m), 4.53 (2H, m), 7.40-7.60 (6H, m), 7.81 (1H, d), 8.60 (1H, br); LRMS ($APCI^+$) 317 [MH^+].

Preparation 9

(3R,4R,5S)-1-{[(3S,4S)-1-Benzyl-4-(5-chloropyridin-2-yl)pyrrolidin-3-yl]carbonyl}-4-(4-fluorophenyl)-3,5-dimethylpiperidin-4-ol

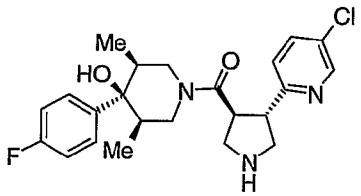


1-Hydroxybenzotriazole (230 mg, 1.7 mmol) and 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (354 mg, 1.8 mmol) were added to a solution of the acid from preparation 8 (522 mg, 1.5

mmol) in dichloromethane (10 mL) and triethylamine (1.03 mL, 7.4 mmol) and the mixture was stirred at room temperature for 30 minutes before the addition of (3*R*,4*s*,5*S*)-4-(4-fluorophenyl)-3,5-dimethylpiperidin-4-ol hydrochloride (prepared according to US 2005/176772) (384 mg, 1.5 mmol). The mixture was stirred at room temperature overnight, the solvent was removed *in vacuo* and the residue was partitioned between ethyl acetate (50 mL) and saturated aqueous sodium hydrogen carbonate (50 mL). The organic layer was washed with brine (50 mL), dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography (silica), eluting with dichloromethane, increasing polarity to 5% methanol in dichloromethane, to give the title compound (546 mg, 71%) as an oil. ^{1}H NMR (CD_3OD, 400 MHz) δ 0.3-0.6 (6H, 4 x d), 1.23 (1H, m), 1.75-1.95 (2H, m), 2.72 (1H, t), 2.85 (1H, m), 2.90-3.20 (3H, m), 3.45-4.05 (5H, m), 4.32 (1H, d), 7.02 (3H, m), 7.20-7.50 (7H, m), 7.80, (1H, dd), 8.50 (1H, d); LRMS (APCI$^+$) 522 [MH$^+$].

Preparation 10

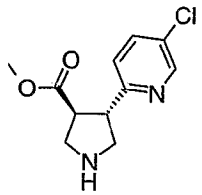
(3R,4R,5S)-1-{[(3S,4S)-4-(5-Chloropyridin-2-yl)pyrrolidin-3-yl]carbonyl}-4-(4-fluorophenyl)-3,5-dimethylpiperidin-4-ol



1-Chloroethyl chloroformate (0.3 mL, 2.8 mmol) was added to a solution of the amide from preparation 9 (370 mg, 0.7 mmol) and N-ethyldiisopropylamine (0.27 mL, 1.6 mmol) in dichloromethane (10 mL) and the mixture was heated at reflux for 3 hours. After cooling to room temperature the solvent was removed *in vacuo* and the residue was partitioned between 10% aqueous citric acid (30 mL) and dichloromethane (30 mL). The organic layer was washed with water (30 mL), dried ($MgSO_4$) and evaporated. The resulting dark oil was taken up in methanol (10 mL) and heated at reflux for 3 hours. The solvent was removed *in vacuo* and the residue was purified by column chromatography (silica) eluting with 5% methanol in dichloromethane, increasing polarity to 10% methanol in dichloromethane, to give the title compound (305 mg, 100%) as an oil. ^{1}H NMR (CD_3OD, 400 MHz) δ 0.4-0.6 (6H, 4 x d), 1.00-1.06, 1.77-1.82 and 1.98-2.05 (2H, 3 x m), 2.76-2.82 (1H, m), 3.00-3.20 (2H, m), 3.40-4.10 (6H, m), 4.36 (1H, m)7.00-7.50 (5H, m), 7.85 and 7.95 (1H, 2 x dd), 8.61 and 8.63 (1H, 2 x d); LRMS (APCI$^+$) 432 [MH$^+$].

Preparation 11

Methyl (3S,4S)-4-(5-chloropyridin-2-yl)pyrrolidine-3-carboxylate

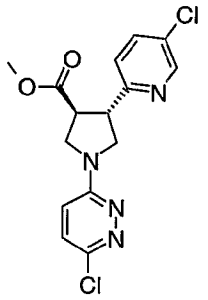


1-Chloroethyl chloroformate (2.33 mL, 21.4 mmol) was added to a solution of the ester from preparation 7 (1.77 g, 5.35 mmol) and N-ethyldiisopropylamine (2.1 mL, 12 mmol) in dichloromethane (10 mL) and

the mixture was heated at reflux for 3 hours. After cooling to room temperature the solvent was removed *in vacuo* and the residue was taken up in methanol (10 mL) and heated at reflux for 16 hours. The solvent was removed *in vacuo* and the residue was purified by column chromatography (silica) eluting with dichloromethane, increasing polarity to 10% methanol in dichloromethane, to give a mixture of the desired product and N-ethyldiisopropylamine as an oil. The oil was taken up in ethyl acetate (30 mL) and the resulting precipitate was filtered. The filtrate was concentrated in vacuo and the residue was taken up in acetonitrile (25 mL). The resulting precipitate was filtered to give the title compound (619 mg, 48%) as a white solid. ^{1}H NMR (CD_3OD, 400 MHz) δ 3.46 (m, 1H), 3.61-3.77 (m, 7H), 3.74 (s, 3H), 3.98 (m, 1H), 7.42 (d. 1H), 7.82 (dd, 1H), 8.57 (d, 1H); LRMS ($APCI^+$) 241 [MH^+].

Preparation 12

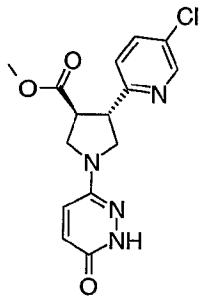
Methyl (3S,4S)-1-(6-chloropyridazin-3-yl)-4-(5-chloropyridin-2-yl)pyrrolidine-3-carboxylate



To a solution of the pyrrolidine from preparation 11 (350 mg, 1.50 mmol) in dimethylsulfoxide (10 mL) was added 3,6-dichloropyridazine (330 mg, 2.20 mmol), triethylamine (0.61 mL, 4.40 mmol), and caesium fluoride (220 mg, 1.45 mmol). The mixture was stirred at 80°C under nitrogen overnight. The reaction mixture was taken up in 25 mL ethyl acetate and washed with 20 mL of water. The organic layer was separated and the aqueous layer was re-extracted with a further 25 mL of ethyl acetate. The combined ethyl acetate extracts were dried over $MgSO_4$, filtered and evaporated to give a pale orange oily solid which was purified by column chromatography, eluting with dichloromethane increasing polarity to 95/5 dichloromethane/methanol. This yielded the title compound as a yellow solid. ^{1}H NMR (CD_3OD, 400 MHz) δ 3.66 (s, 1H), 3.72 (m, 1H), 3.78 (t, 1H), 3.96-4.12 (m, 4H), 7.04 (d, 1H), 7.42 (m, 2H), 7.79 (d, 1H), 8.52 (s, 1H); LRMS (EI^+) 353 [MH^+].

Preparation 13

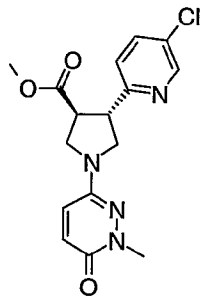
Methyl (3S,4S)-4-(5-chloropyridin-2-yl)-1-(6-oxo-1,6-dihydropyridazin-3-yl)pyrrolidine-3-carboxylate



A solution of chloropyridazine from preparation 12 (803 mg, 2.27 mmol) was dissolved in deoxygenated acetic acid and heated at reflux under nitrogen for 44 hours. The solvent was removed *in vacuo* and 15 mL methanol was added. HCl gas was then bubbled through the reaction mixture until it was saturated and the mixture was stirred under a drying tube overnight. The methanol was removed *in vacuo* and the residue was partitioned between DCM and 10% K_2CO_3. The organic layer was separated, dried over $MgSO_4$, filtered and evaporated to yield the title compound as a pale brown solid (577 mg, 76%). ^1H NMR (CD_3OD, 400 MHz) δ 3.58-3.76 and 3.83-3.97 (6H, 2 x m), 3.65 (3H, s), 6.89 (1H, d), 7.31 (1H, d), 7.39 (1H, d), 7.79 (1H, dd), 8.52 (1H, d); LRMS (EI^+) 335 [MH^+].

Preparation 14

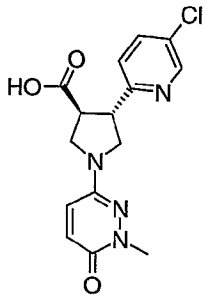
Methyl (3S,4S)-4-(5-chloropyridin-2-yl)-1-(1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)pyrrolidine-3-carboxylate



To a solution of the pyridazinone from preparation 13 (557 mg, 1.66 mmol) in dimethylformamide (10 mL) was added sodium hexamethydisilazide (1M in tetrahydrofuran, 2.00 mL, 2.00 mmol) and lithium bromide (173 mg, 2.00 mmol). The reaction was stirred under nitrogen for 10 minutes before iodomethane (0.083 mL, 1.30 mmol) was added. The reaction was stirred under nitrogen for 4 hours and then partitioned between ethyl acetate (30 mL) and water (30 mL). The organic layer was separated, dried over $MgSO_4$, filtered and evaporated to give a brown oil which was purified using column chromatography (silica), eluting with 100% dichloromethane, increasing polarity to 95/5 dichloromethane/methanol. This yielded the title compound as a yellow oil (500 mg, 90%). ^1H NMR (CD_3OD, 400 MHz) δ 3.64 (m, 9H), 3.92 (m, 3H), 6.87 (d, 1H), 7.26 (d, 1H), 7.37 (d, 1H), 7.79 (dd, 1H), 8.51 (s, 1H); LRMS (EI^+) 349 [MH^+].

Preparation 15

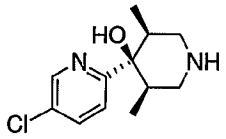
(3S,4S)-4-(5-Chloropyridin-2-yl)-1-(1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)pyrrolidine-3-carboxylic acid



To a solution of the ester from preparation 14 (500 mg, 1.43 mmol) in dioxane (10 mL) was added sodium hydroxide (172 mg, 4.30 mmol) as a solution in 5 mL of water. The reaction was stirred under a drying tube overnight. The solvent was removed *in vacuo*, the residue was taken up in water, neutralised with 4 equiv. of 2M HCl and evaporated. The residue was stirred with 20 mL of acetonitrile and filtered to give a buff solid (512 mg containing 3 equiv. NaCl - 338mg product + 174mg NaCl). ^{1}H NMR (CD_3OD, 400 MHz) δ 3.6 (m, 2H), 3.64 (s, 3H), 3.7 (t, 1H), 3.9 (m, 3H), 6.88 (d, 1H), 7.27 (d, 1H), 7.41 (d, 1H), 7.79 (dd, 1H), 8.52 (s, 1H); LRMS (EI^+) 335 [MH^+].

Preparation 16

(3R,4s,5S)-4-(5-chloropyridin-2-yl)-3,5-dimethylpiperidin-4-ol



Step A: (3R,4s,5S)-4-(5-chloropyridin-2-yl)-1-(4-methoxybenzyl)-3,5-dimethylpiperidin-4-ol

A solution of 2-bromo-5-chloropyridine (6.0 g, 31.2 mmol) in toluene (90 mL) was cooled to −78°C under nitrogen. *n*-Butyllithium (2.5M in hexanes) (15 mL, 37.5 mmol) was added dropwise over 12 minutes and the mixture was stirred at −78°C for 1 hour. A solution of (3*R*,5*S*)-1-(4-methoxybenzyl)-3,5-dimethylpiperidin-4-one (prepared according to international patent application publication number WO 2005/077935) (6.93 g, 28.1 mmol) in toluene (15 mL) was then added dropwise over 10 minutes and the mixture was stirred at −78°C for a further 3 hours before being allowed to warm to room temperature. The mixture was quenched by pouring into saturated ammonium chloride (100 mL) and, after stirring for 5 minutes, the mixture was partitioned between water (50 mL) and ethyl acetate (300 mL). The organic phase was separated and the aqueous phase was extracted with further ethyl acetate (2 x 300 mL). The combined organic extracts were dried over magnesium sulfate, filtered and then evaporated to dryness to give the crude intermediate. Purification by column chromatography (silica) eluting with 2% methanol in dichloromethane, increasing polarity to 10% (10:1 methanol:880 ammonia) in dichloromethane, gave (3R,4s,5S)-4-(5-chloropyridin-2-yl)-1-(4-methoxybenzyl)-3,5-dimethylpiperidin-4-ol as an orange oil (8.48 g, 83%).

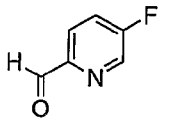
Step B: (3R,4s,5S)-4-(5-chloropyridin-2-yl)-3,5-dimethylpiperidin-4-ol

The product from step A (6.56 g, 18.2 mmol) was dissolved in dry dichloromethane (100 mL), triethylamine (2.02 g, 20.0 mmol) was added and the solution was cooled to 5°C under nitrogen. 1-Chloroethylchloroformate (3.1 g, 21.9 mmol) was added dropwise to the stirred solution and on completion of addition the mixture was stirred for a further 2.5 hours at room temperature. The mixture was then washed with 10% aqueous potassium carbonate solution (3 x 50 mL) dried over magnesium sulfate and evaporated to dryness. The crude oil was heated under reflux in methanol (100 mL) for 2.5 hours and the solvent was removed *in vacuo*. The residue was dissolved in dichloromethane (100 mL) and methanol (10 mL), solid potassium carbonate (10 g) was added and the heterogeneous mixture was stirred for 30 minutes. The solid potassium carbonate was filtered off and the filtrate was evaporated to dryness. The crude product was then purified by column chromatography (silica) eluting with 10% methanol in dichloromethane, increasing polarity to 20% (10:1 methanol:880 ammonia) in

dichloromethane, to give the title compound (3.37 g, 77%) as a yellowish solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.53 (3H, s), 0.57 (s, 3H), 2.60-2.71 (m, 2H), 3.13 (q, 2H), 3.32 (d, 2H), 7.43 (d, 1H), 7.78 (dd, 1H), 8.50 (1H, d), 9.58 (br, 1H), 9.84 (br, 1H); LRMS (APCI+) 241 and 243 [MH^+].

Preparation 17

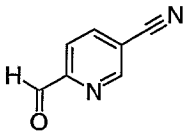
5-Fluoropyridine-2-carbaldehyde



The title compound was prepared according to the methods of preparations 1 and 2, starting from 2-bromo-5-fluoropyridine. This gave crude material containing tetrahydrofuran and diethyl ether which was used without further purification. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.57 (1H, dt), 8.03 (1H, dd), 8.62 (1H, d), 10.04 (1H, s); LRMS (APCI$^+$) 126 [MH^+].

Preparation 18

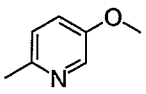
6-Formylnicotinonitrile



A mixture of 6-methylnicotinonitrile (10.0 g, 84.6 mmol) and iodine (20.0 g, 78.8 mmol) in dimethylsulfoxide (150 mL) was heated at 150°C under nitrogen for 20 minutes (reaction exhaust was scrubbed with bleach to remove dimethyl sulfide). After cooling to room temperature saturated aqueous sodium bicarbonate (200 mL) was added carefully and the resulting mixture was extracted with toluene (3 x 100 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated to give the desired product as an orange oil (5.65 g, 50%) which was used without further purification. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.06 (1H, d), 8.17 (1H, dd), 9.05 (1H, d), 10.12 (1H, s).

Preparation 19

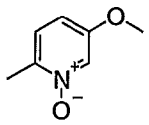
5-Methoxy-2-methylpyridine



6-methylpyridin-3-ol (50.0 g, 0.458 mol) was added to a suspension of powdered KOH (103 g, 1.83 mol) in dimethylsulfoxide (750 mL) and the mixture was left to stir at room temperature under nitrogen for 1.5 hours. Methyl iodide (30 mL, 68.3 g, 0.481 mol) was then added dropwise over 1 hour to the dark brown mixture (exothermic). After stirring at room temperature for 1.5 hours water (1.0 L) was added and the mixture was extracted with ethyl acetate (2 x 300 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated at 40°C on a rotary evaporator. The residue was purified by column chromatography (silica), eluting with pentane, increasing polarity to ethyl acetate, to give the volatile product as a ~1:1 mixture with ethyl acetate (40 g, ~23.3 g product, 41%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.45 (3H, s), 3.79 (3H, s), 7.02 (1H, d), 7.08 (1H, dd), 8.16 (1H, d).

Preparation 20

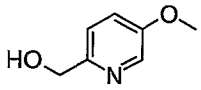
5-Methoxy-2-methylpyridine 1-oxide



m-Chloroperbenzoic acid (51.3 g, 0.297 mol) was added portionwise to a solution of the compound of preparation 19 (40 g of a 1:1 mixture with ethyl acetate, 23.3 g, 189 mmol) in dichloromethane (1500 mL) and the mixture was stirred at room temperature for 2 hours. A solution of sodium sulfite (45 g) in water (250 mL) was then added to the reaction and the mixture was stirred for 15 minutes, at which point starch/KI indicator paper gave a negative test for the presence of oxidant. The organic layer was separated, dried over $MgSO_4$ and evaporated to give a pale yellow solid (54 g) which was a ~1:1 mixture of the desired product and m-chlorobenzoic acid (mCBA). This was taken on to the following step without further purification. ^1H NMR ($CDCl_3$, 400 MHz) δ 3.84 (3H, s), 6.97 (1H, dd), 7.19 (1H, d), 7.34 (1H, t, mCBA), 7.48 (1H, d, mCBA), 7.94 (1H, d, mCBA), 8.04 (1H, s, mCBA), 8.36 (1H, d).

Preparation 21

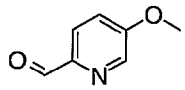
(5-Methoxypyridin-2-yl)methanol



Trifluoroacetic anhydride (28.2 mL, 203 mmol) was added dropwise to an ice cooled solution of the product from preparation 20 (~135 mmol) in dichloromethane (500 mL), the mixture was allowed to warm to room temperature and stirred overnight. Tlc analysis indicated still largely starting material so a further portion of trifluoroacetic anhydride (15 mL, 108 mmol) was added dropwise and the mixture was allowed to stir for a further 27 hours. The reaction was quenched by the cautious addition of methanol (250 mL) and left to stir for 30 minutes before being concentrated in vacuo. 2.5 M sodium hydroxide (100 mL) was then added cautiously and the mixture was extracted with dichloromethane (4 x 100 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated to give the desired product (12 g, 64%) contaminated with recovered starting material (~15 mol%). ^1H NMR ($CDCl_3$, 400 MHz) δ 3.80 (3H, s), 4.40 (1H, br), 4.66 (2H, s), 7.16 (1H, dd), 7.20 (1H, d), 8.17 (1H, d).

Preparation 22

5-Methoxypyridine-2-carbaldehyde

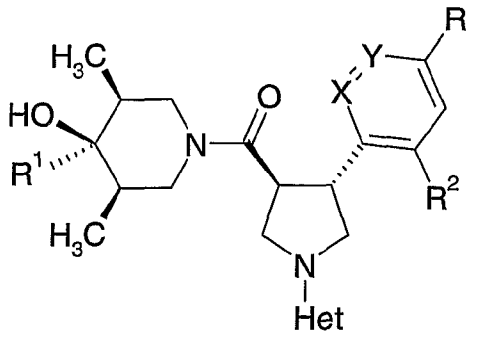


MnO_2 (97.0 g, 360 mmol) was added in one portion to a solution of the alcohol from preparation 21 (12 g, 86 mmol) in dichloromethane (500 mL) and the resulting suspension was stirred at room temperature for 64 hours. The reaction mixture was filtered through Celite® and the solvent was removed in vacuo to give the desired product (8.6 g, 73%) contaminated with 5-methoxy-2-methylpyridine 1-oxide (15 mol%)

as an orange oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.93 (3H, s), 7.26 (1H, dd), 7.91 (1H, d), 8.37 (1H, d), 9.94 (1H, s).

CLAIMS

1. A compound of formula (I):



(I)

wherein

one of X and Y is N and the other is CH,

R is F, Cl, CN, CF_3 or methoxy, with the proviso that when Y is N, R is not F or Cl,

R^1 is phenyl, 2-pyridyl, C_3-C_6 cycloalkyl or CH_2(C_3-C_6 cycloalkyl), wherein the ring moiety is optionally substituted by one or more substituents independently selected from F, Cl, CN, methyl and methoxy,

R^2 is H, F or Cl, with the proviso that when Y is N, R^2 is not F or Cl,

Het is a 6-membered ring containing one or 2 N atoms, wherein the ring is either aromatic, or contains 2 double bonds in the ring and a =O substituent, which ring is optionally substituted by one or more substituents independently selected from F, Cl, OH, CN, methyl, ethyl, NH_2, $NHCH_3$, $N(CH_3)_2$ and methoxy,
or alternatively, Het is a 6-membered ring containing one or 2 N atoms fused at the 3,4-positions, relative to the attachment to the pyrrolidine ring, to a 5-membered aromatic ring containing one or two further N atoms, which 5-membered ring is optionally substituted by OH,
and the pharmaceutically acceptable salts, solvates (including hydrates), and prodrugs thereof.

2. A compound according to claim 1 wherein X is N and Y is CH, and the pharmaceutically acceptable salts, solvates (including hydrates), and prodrugs thereof.

3. A compound according to any one of claims 1 or 2 wherein R is chloro, and the pharmaceutically acceptable salts, solvates (including hydrates), and prodrugs thereof.

4. A compound according to any one of claims 1, 2 or 3, and the pharmaceutically acceptable salts, solvates (including hydrates), and prodrugs thereof, wherein
R^1 is phenyl optionally substituted by one or more substituents independently selected from F, Cl, CN, methyl and methoxy.

5. A compound according to claim 4, and the pharmaceutically acceptable salts, solvates (including hydrates), and prodrugs thereof, wherein R^1 is phenyl, 4-chlorophenyl or 4-fluorophenyl.

6. A compound according to any on of claims 1, 2 or 3, and the pharmaceutically acceptable salts, solvates (including hydrates), and prodrugs thereof, wherein
R^1 is C_3-C_6 cycloalkyl.

7. A compound according to any on of claim 6, and the pharmaceutically acceptable salts, solvates (including hydrates), and prodrugs thereof, wherein
R^1 is cyclopropyl or cyclohexyl.

8. A compound according to any one of claims 1, 2, 3, 4, 5, 6 or 7, and the pharmaceutically acceptable salts, solvates (including hydrates), and prodrugs thereof, wherein R^2 is H or F.

9. A compound according to claim 8, and the pharmaceutically acceptable salts, solvates (including hydrates), and prodrugs thereof, wherein R^2 is H.

10. A compound according to any one of claims 1, 2, 3, 4, 5, 6, 7, 8 or 9, and the pharmaceutically acceptable salts, solvates (including hydrates), and prodrugs thereof, wherein
Het is pyridin-2-yl, pyridin-3-yl, pyridazin-3-yl, 6-oxo-1,6-dihydropyridazin-3-yl, 6-oxo-1,6-dihydropyridin-3-yl, 2-oxo-1,2-dihydropyrimidin-4-yl, 6-oxo-1,6-dihydropyrimidin-4-yl, 2-oxo-1,2-dihydropyridin-4-yl, imidazo[1,2-b]pyridazin-6-yl, [1,2,4]triazolo[4,3-b]pyridazin-6-yl or 6-oxo-1,6-dihydropyridin-2-yl, optionally substituted by one or more substituents independently selected from F, Cl, OH, CN, methyl, ethyl and methoxy.

11. A compound according to claim 10, and the pharmaceutically acceptable salts, solvates (including hydrates), and prodrugs thereof, wherein Het is pyridin-2-yl, pyridin-3-yl, pyridazin-3-yl or 6-oxo-1,6-dihydropyridazin-3-yl, optionally substituted by one or more substituents independently selected from OH, CN, F, methyl and methoxy.

12. A compound according to claim 11, and the pharmaceutically acceptable salts, solvates (including hydrates), and prodrugs thereof, wherein Het is pyridin-2-yl or pyridazin-3-yl, each of which is substituted at the para-position relative to the bond linking to the pyrrolidine moiety, by OH, CN or methoxy.

13. A compound according to claim 12, and the pharmaceutically acceptable salts, solvates (including hydrates), and prodrugs thereof, wherein Het is pyridazin-3-yl substituted at the para-position relative to the bond linking to the pyrrolidine moiety, by OH, CN or methoxy.

14. A compound according to claim 1 selected from:
6-[(3S,4S)-3-(5-chloropyridin-2-yl)-4-{[(3R,4R,5S)-4-(4-fluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]pyridazine-3-carbonitrile;
6-[(3S,4S)-3-(5-chloropyridin-2-yl)-4-{[(3R,4R,5S)-4-hydroxy-3,5-dimethyl-4-phenylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]pyridazine-3-carbonitrile;
6-[(3S,4S)-3-(5-chloropyridin-2-yl)-4-{[(3R,4R,5S)-4-hydroxy-3,5-dimethyl-4-pyridin-2-ylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]pyridazine-3-carbonitrile;
6-[(3S,4S)-3-(5-chloropyridin-2-yl)-4-{[(3R,4R,5S)-4-hydroxy-3,5-dimethyl-4-phenylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]pyridazin-3(2H)-one;
6-[(3S,4S)-3-(5-chloropyridin-2-yl)-4-{[(3R,4R,5S)-4-hydroxy-3,5-dimethyl-4-phenylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]-2-methylpyridazin-3(2H)-one;
6-[(3S,4S)-3-{[(3R,4R,5S)-4-(4-chlorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}-4-(5-chloropyridin-2-yl)pyrrolidin-1-yl]-2-methylpyridazin-3(2H)-one;
6-[(3S,4S)-3-(5-chloropyridin-2-yl)-4-{[(3R,4R,5S)-4-(5-chloropyridin-2-yl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]-2-methylpyridazin-3(2H)-one;
6-[(3S,4S)-3-(5-chloropyridin-2-yl)-4-{[(3R,4R,5S)-4-(3,4-difluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]-2-methylpyridazin-3(2H)-one;
6-[(3S,4S)-3-(5-chloropyridin-2-yl)-4-{[(3R,4R,5S)-4-hydroxy-4-(4-methoxyphenyl)-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]-2-methylpyridazin-3(2H)-one;
6-[(3S,4S)-3-(5-chloropyridin-2-yl)-4-{[(3R,4R,5S)-4-cyclohexyl-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]-2-methylpyridazin-3(2H)-one;
(3R,4R,5S)-1-{[(3S,4S)-1-(6-chloropyridazin-3-yl)-4-(5-chloropyridin-2-yl)pyrrolidin-3-yl]carbonyl}-4-(4-fluorophenyl)-3,5-dimethylpiperidin-4-ol;
(3R,4R,5S)-1-{[(3S,4S)-4-(5-chloropyridin-2-yl)-1-(6-methoxypyridazin-3-yl)pyrrolidin-3-yl]carbonyl}-4-cyclopropyl-3,5-dimethylpiperidin-4-ol;
(3R,4R,5S)-1-{[(3S,4S)-4-(5-chloropyridin-2-yl)-1-(5-fluoropyridin-3-yl)pyrrolidin-3-yl]carbonyl}-4-(4-fluorophenyl)-3,5-dimethylpiperidin-4-ol;
6-[(3S,4S)-3-(5-chloropyridin-2-yl)-4-{[(3R,4R,5S)-4-(4-fluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]nicotinonitrile;
6-[(3S,4S)-3-{[(3R,4R,5S)-4-(4-fluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}-4-(5-fluoropyridin-2-yl)pyrrolidin-1-yl]pyridazine-3-carbonitrile;
6-[(3S,4S)-3-(5-fluoropyridin-2-yl)-4-{[(3R,4R,5S)-4-hydroxy-3,5-dimethyl-4-phenylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]pyridazine-3-carbonitrile;
6-[(3S,4S)-3-{[(3R,4R,5S)-4-(4-chlorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}-4-(5-fluoropyridin-2-yl)pyrrolidin-1-yl]pyridazine-3-carbonitrile;
6-[(3S,4S)-3-{[(3R,4R,5S)-4-(4-chlorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}-4-(5-fluoropyridin-2-yl)pyrrolidin-1-yl]pyridazin-3(2H)-one;

6-[(3S,4S)-3-(5-cyanopyridin-2-yl)-4-{[(3R,4R,5S)-4-(4-fluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]pyridazine-3-carbonitrile;

6-[(3S,4R)-3-{[(3R,4R,5S)-4-(4-fluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}-4-(6-methoxypyridin-3-yl)pyrrolidin-1-yl]pyridazine-3-carbonitrile;

6-[(3S,4S)-3-{[(3R,4R,5S)-4-(4-fluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}-4-(5-methoxypyridin-2-yl)pyrrolidin-1-yl]pyridazine-3-carbonitrile;

(3R,4R,5S)-4-(4-fluorophenyl)-1-{[(3S,4R)-1-(5-fluoropyridin-3-yl)-4-(6-methoxypyridin-3-yl)pyrrolidin-3-yl]carbonyl}-3,5-dimethylpiperidin-4-ol;

(3R,4R,5S)-1-{[(3S,4S)-4-(5-chloropyridin-2-yl)-1-pyridazin-3-ylpyrrolidin-3-yl]carbonyl}-4-(4-fluorophenyl)-3,5-dimethylpiperidin-4-ol;

6-[(3S,4S)-3-(5-chloropyridin-2-yl)-4-{[(3R,4R,5S)-4-(4-fluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]pyridazin-3(2H)-one;

6-[(3S,4S)-3-(5-chloropyridin-2-yl)-4-{[(3R,4R,5S)-4-(4-fluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]-2-methylpyridazin-3(2H)-one;

(3R,4R,5S)-1-{[(3S,4S)-4-(5-chloropyridin-2-yl)-1-[1,2,4]triazolo[4,3-b]pyridazin-6-ylpyrrolidin-3-yl]carbonyl}-4-(4-fluorophenyl)-3,5-dimethylpiperidin-4-ol;

(3R,4R,5S)-1-{[(3S,4S)-4-(5-chloropyridin-2-yl)-1-imidazo[1,2-b]pyridazin-6-ylpyrrolidin-3-yl]carbonyl}-4-(4-fluorophenyl)-3,5-dimethylpiperidin-4-ol;

4-[(3S,4S)-3-(5-chloropyridin-2-yl)-4-{[(3R,4R,5S)-4-(4-fluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]pyrimidin-2(1H)-one;

4-[(3S,4S)-3-(5-chloropyridin-2-yl)-4-{[(3R,4R,5S)-4-(4-fluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]-1-methylpyrimidin-2(1H)-one;

(3R,4R,5S)-1-{[(3S,4S)-4-(5-chloropyridin-2-yl)-1-(6-methoxypyridazin-3-yl)pyrrolidin-3-yl]carbonyl}-4-(4-fluorophenyl)-3,5-dimethylpiperidin-4-ol;

6-[(3S,4S)-3-(5-chloro-3-fluoropyridin-2-yl)-4-{[(3R,4R,5S)-4-(4-fluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]pyridazine-3-carbonitrile;

6-[(3S,4S)-3-(5-chloro-3-fluoropyridin-2-yl)-4-{[(3R,4R,5S)-4-(4-fluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]pyridazin-3(2H)-one;

6-[(3S,4S)-3-(5-chloro-3-fluoropyridin-2-yl)-4-{[(3R,4R,5S)-4-(4-fluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]-2-methylpyridazin-3(2H)-one;

6-[(3S,4S)-3-(3,5-difluoropyridin-2-yl)-4-{[(3R,4R,5S)-4-(4-fluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]pyridazine-3-carbonitrile;

6-[(3S,4S)-3-(3,5-difluoropyridin-2-yl)-4-{[(3R,4R,5S)-4-(4-fluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]pyridazin-3(2H)-one;

6-[(3S,4S)-3-(3,5-difluoropyridin-2-yl)-4-{[(3R,4R,5S)-4-(4-fluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]-2-methylpyridazin-3(2H)-one;

6-[(3S,4S)-3-{[(3R,4R,5S)-4-(4-chlorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}-4-(5-chloropyridin-2-yl)pyrrolidin-1-yl]pyridazine-3-carbonitrile;

6-[(3S,4S)-3-(5-chloropyridin-2-yl)-4-{[(3R,4R,5S)-4-(3,4-difluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]pyridazine-3-carbonitrile;

6-[(3S,4S)-3-{[(3R,4R,5S)-4-(4-chlorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}-4-(5-chloropyridin-2-yl)pyrrolidin-1-yl]pyridazin-3(2H)-one;
6-[(3S,4S)-3-(5-chloropyridin-2-yl)-4-{[(3R,4R,5S)-4-(3,4-difluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]pyridazin-3(2H)-one;
and the pharmaceutically acceptable salts, solvates (including hydrates), and prodrugs thereof.

15. A compound according to claim 14 selected from:
6-[(3S,4S)-3-(5-chloropyridin-2-yl)-4-{[(3R,4R,5S)-4-(4-fluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]pyridazine-3-carbonitrile;
6-[(3S,4S)-3-(5-chloropyridin-2-yl)-4-{[(3R,4R,5S)-4-hydroxy-3,5-dimethyl-4-phenylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]pyridazine-3-carbonitrile;
6-[(3S,4S)-3-(5-chloropyridin-2-yl)-4-{[(3R,4R,5S)-4-hydroxy-3,5-dimethyl-4-phenylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]pyridazin-3(2H)-one;
6-[(3S,4S)-3-(5-chloropyridin-2-yl)-4-{[(3R,4R,5S)-4-hydroxy-3,5-dimethyl-4-phenylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]-2-methylpyridazin-3(2H)-one;
6-[(3S,4S)-3-{[(3R,4R,5S)-4-(4-chlorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}-4-(5-chloropyridin-2-yl)pyrrolidin-1-yl]-2-methylpyridazin-3(2H)-one;
6-[(3S,4S)-3-(5-chloropyridin-2-yl)-4-{[(3R,4R,5S)-4-(5-chloropyridin-2-yl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]-2-methylpyridazin-3(2H)-one;
6-[(3S,4S)-3-(5-chloropyridin-2-yl)-4-{[(3R,4R,5S)-4-(3,4-difluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]-2-methylpyridazin-3(2H)-one;
(3R,4R,5S)-1-{[(3S,4S)-4-(5-chloropyridin-2-yl)-1-pyridazin-3-ylpyrrolidin-3-yl]carbonyl}-4-(4-fluorophenyl)-3,5-dimethylpiperidin-4-ol;
6-[(3S,4S)-3-(5-chloropyridin-2-yl)-4-{[(3R,4R,5S)-4-(4-fluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]pyridazin-3(2H)-one;
6-[(3S,4S)-3-(5-chloropyridin-2-yl)-4-{[(3R,4R,5S)-4-(4-fluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]-2-methylpyridazin-3(2H)-one;
(3R,4R,5S)-1-{[(3S,4S)-4-(5-chloropyridin-2-yl)-1-[1,2,4]triazolo[4,3-b]pyridazin-6-ylpyrrolidin-3-yl]carbonyl}-4-(4-fluorophenyl)-3,5-dimethylpiperidin-4-ol;
(3R,4R,5S)-1-{[(3S,4S)-4-(5-chloropyridin-2-yl)-1-imidazo[1,2-b]pyridazin-6-ylpyrrolidin-3-yl]carbonyl}-4-(4-fluorophenyl)-3,5-dimethylpiperidin-4-ol;
4-[(3S,4S)-3-(5-chloropyridin-2-yl)-4-{[(3R,4R,5S)-4-(4-fluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]pyrimidin-2(1H)-one;
4-[(3S,4S)-3-(5-chloropyridin-2-yl)-4-{[(3R,4R,5S)-4-(4-fluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]-1-methylpyrimidin-2(1H)-one;
6-[(3S,4S)-3-(5-chloro-3-fluoropyridin-2-yl)-4-{[(3R,4R,5S)-4-(4-fluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]pyridazine-3-carbonitrile;
6-[(3S,4S)-3-(5-chloro-3-fluoropyridin-2-yl)-4-{[(3R,4R,5S)-4-(4-fluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]pyridazin-3(2H)-one;
6-[(3S,4S)-3-(5-chloro-3-fluoropyridin-2-yl)-4-{[(3R,4R,5S)-4-(4-fluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]-2-methylpyridazin-3(2H)-one;

6-[(3S,4S)-3-(3,5-difluoropyridin-2-yl)-4-{[(3R,4R,5S)-4-(4-fluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]pyridazine-3-carbonitrile;
6-[(3S,4S)-3-(3,5-difluoropyridin-2-yl)-4-{[(3R,4R,5S)-4-(4-fluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]pyridazin-3(2H)-one;
6-[(3S,4S)-3-(3,5-difluoropyridin-2-yl)-4-{[(3R,4R,5S)-4-(4-fluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]-2-methylpyridazin-3(2H)-one;
6-[(3S,4S)-3-{[(3R,4R,5S)-4-(4-chlorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}-4-(5-chloropyridin-2-yl)pyrrolidin-1-yl]pyridazine-3-carbonitrile;
6-[(3S,4S)-3-(5-chloropyridin-2-yl)-4-{[(3R,4R,5S)-4-(3,4-difluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]pyridazine-3-carbonitrile;
6-[(3S,4S)-3-{[(3R,4R,5S)-4-(4-chlorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}-4-(5-chloropyridin-2-yl)pyrrolidin-1-yl]pyridazin-3(2H)-one;
6-[(3S,4S)-3-(5-chloropyridin-2-yl)-4-{[(3R,4R,5S)-4-(3,4-difluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]pyridazin-3(2H)-one;
and the pharmaceutically acceptable salts, solvates (including hydrates), and prodrugs thereof.

16. A compound according to claim 15 selected from:
6-[(3S,4S)-3-(5-chloropyridin-2-yl)-4-{[(3R,4R,5S)-4-(4-fluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]pyridazine-3-carbonitrile;
6-[(3S,4S)-3-{[(3R,4R,5S)-4-(4-chlorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}-4-(5-chloropyridin-2-yl)pyrrolidin-1-yl]-2-methylpyridazin-3(2H)-one;
6-[(3S,4S)-3-(5-chloropyridin-2-yl)-4-{[(3R,4R,5S)-4-(5-chloropyridin-2-yl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]-2-methylpyridazin-3(2H)-one;
6-[(3S,4S)-3-(5-chloropyridin-2-yl)-4-{[(3R,4R,5S)-4-(3,4-difluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]-2-methylpyridazin-3(2H)-one;
6-[(3S,4S)-3-(5-chloropyridin-2-yl)-4-{[(3R,4R,5S)-4-(4-fluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]pyridazin-3(2H)-one;
6-[(3S,4S)-3-(5-chloropyridin-2-yl)-4-{[(3R,4R,5S)-4-(4-fluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]-2-methylpyridazin-3(2H)-one;
6-[(3S,4S)-3-{[(3R,4R,5S)-4-(4-chlorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}-4-(5-chloropyridin-2-yl)pyrrolidin-1-yl]pyridazine-3-carbonitrile;
6-[(3S,4S)-3-(5-chloropyridin-2-yl)-4-{[(3R,4R,5S)-4-(3,4-difluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]pyridazine-3-carbonitrile;
6-[(3S,4S)-3-{[(3R,4R,5S)-4-(4-chlorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}-4-(5-chloropyridin-2-yl)pyrrolidin-1-yl]pyridazin-3(2H)-one;
6-[(3S,4S)-3-(5-chloropyridin-2-yl)-4-{[(3R,4R,5S)-4-(3,4-difluorophenyl)-4-hydroxy-3,5-dimethylpiperidin-1-yl]carbonyl}pyrrolidin-1-yl]pyridazin-3(2H)-one;
and the pharmaceutically acceptable salts, solvates (including hydrates), and prodrugs thereof.

17. A pharmaceutical composition comprising a compound according to any one of claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or 16, or a pharmaceutically acceptable salt, solvate (including hydrate), or prodrug thereof, and a pharmaceutically acceptable diluent, carrier or adjuvant.

18. A compound according to any one of claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or 16, or a pharmaceutically acceptable salt, solvate (including hydrate), or prodrug thereof, for use as a medicament.

19. A compound according to any one of claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or 16, or a pharmaceutically acceptable salt, solvate (including hydrate), or prodrug thereof, for use as a medicament for the treatment of a disorder which would benefit from MC4 agonism.

20. A compound according to any one of claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or 16, or a pharmaceutically acceptable salt, solvate (including hydrate), or prodrug thereof, for use as a medicament for the treatment of a condition which would benefit from treatment with a MC4 receptor agonist, such as sexual dysfunction, obesity, diabetes or a urological condition.

21. A method of treating a disorder which would benefit from agonism of the MC4 receptor which comprises adiministration of a therapeutically effective amount of a compound, salt, solvate or prodrug according to any one of claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or 16, or a pharmaceutically acceptable salt, solvate (including hydrate), or prodrug thereof, or pharmaceutical composition thereof, to a patient in need thereof.

22. A method according to claim 21 wherein the disorder is a sexual dysfunction, obesity, diabetes or a urological condition.

23. A compound, salt, solvate, prodrug, process, method of treatment, pharmaceutical composition, substantially as described herein.

Figure 1

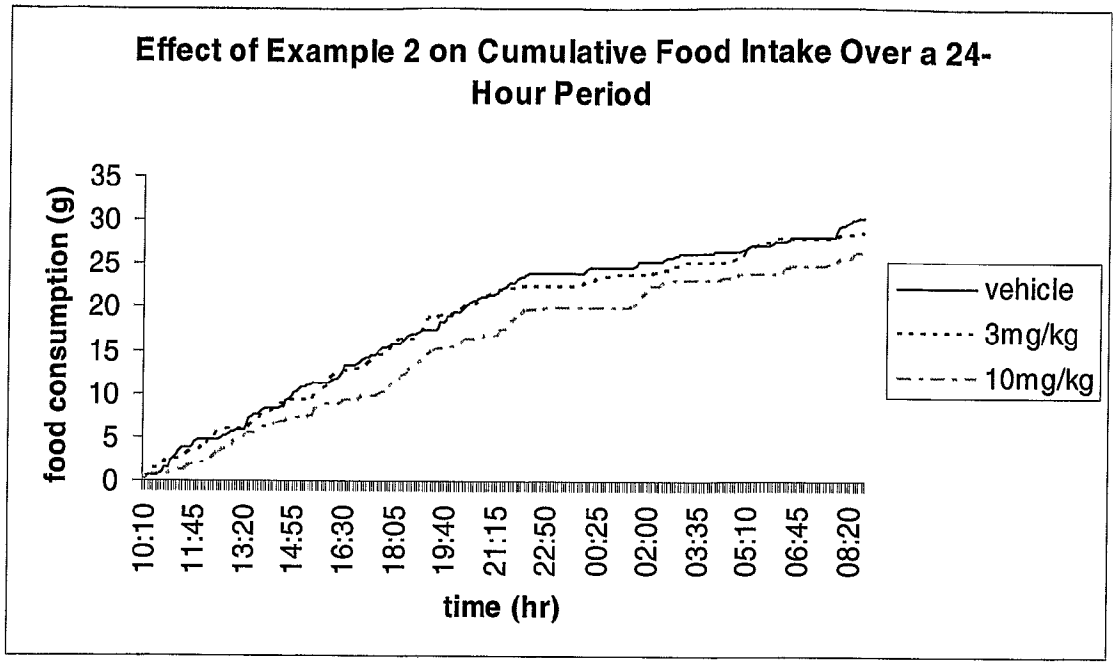
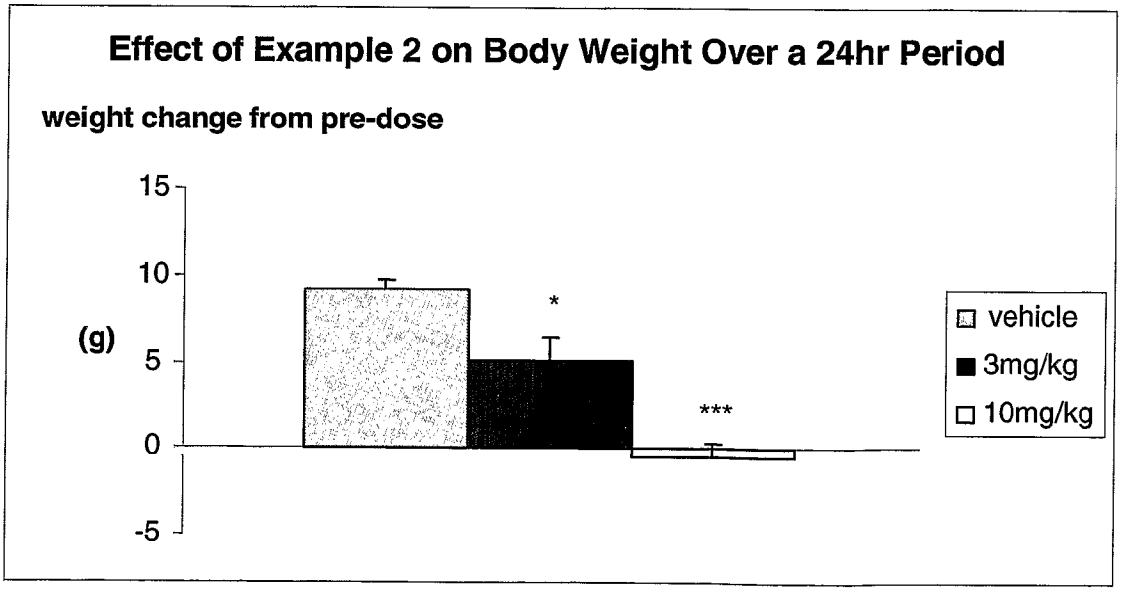


Figure 2



Electronic Acknowledgement Receipt

EFS ID:	20112305
Application Number:	14069927
International Application Number:	
Confirmation Number:	3207
Title of Invention:	COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING
First Named Inventor/Applicant Name:	Fabio TRENTO
Customer Number:	6980
Filer:	Clark G. Sullivan/Angelina Stantini
Filer Authorized By:	Clark G. Sullivan
Attorney Docket Number:	244168.000015US4
Receipt Date:	11-SEP-2014
Filing Date:	01-NOV-2013
Time Stamp:	15:00:21
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	US4PTO-IDSTRANS-15.PDF	83410 1aa88df3c8b05c27fe209c724e18eae5bb36354a	no	4

Warnings:	
Information:	

2	Information Disclosure Statement (IDS) Form (SB08)	US4PTO-IDSSB08-15.PDF	628312 dac16e5686bc29524c1e8f0b50ffad3f73d5dc5f	no	4
Warnings:					
Information:					
3	Foreign Reference	US3US4US5-ART-WO2007096763.PDF	6695910 f73adf78ef3cf0d3e52963c232b650e26b0618d6	no	71
Warnings:					
Information:					
4	Non Patent Literature	US3US4US5-ART-NPL-EPSR1-15.PDF	364367 a58e4d61644ab9580e92abbdb66f7d6419c7cd56	no	7
Warnings:					
Information:					
5	Non Patent Literature	US3US4US5-ART-NPL-EPSR2-15.PDF	528189 4b0088568d063fc4a0a18bd3445180b16b1ed60b	no	10
Warnings:					
Information:					
6	Non Patent Literature	US3US4US5-ART-NPL-EPSR3-15.PDF	383012 f761172b971ae950fbfd76e520d5d0b0372f4900	no	8
Warnings:					
Information:					
		Total Files Size (in bytes):	8683200		

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

New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

Docket No.: 244168.000015US4
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Fabio TRENTO	Customer No.: 06980
Application No.: 14/069,927	Confirmation No.: 3207
Filing Date: November 1, 2013	Art Unit: 1612
For: COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING	Examiner: Walter E. WEBB

INFORMATION DISCLOSURE STATEMENT (IDS)

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

Dear Sir:

This Information Disclosure Statement is submitted in accordance with 37 C.F.R. 1.97, 1.98, and it is requested that the information set forth in this statement and in the listed documents be considered during the pendency of the above-identified application, and any other application relying on the filing date of the above-identified application or cross-referencing it as a related application.

1. This IDS should be considered, in accordance with 37 C.F.R. 1.97, as it is filed: (Check one of the boxes A-D)

- ☐ A. within three months of the filing date of the above-identified national application or within three months of the entry into the national stage of the above identified national application
- ☒ **B. before the mailing date of a first office action on the merits, or a first office action after filing a request for continued examination.**
- ☐ C. after (A) and (B) above, but before final rejection or allowance, and Applicant has made the necessary statement in box "i" below or paid the necessary fee in box "ii" below.

(check one of the boxes "i" and "ii" below:)

☐ i. Counsel states that, upon information and belief, each item of information listed herein was (check one of boxes (a) or (b))

☐ (a) 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 this IDS; or

☐ (b) not cited in a communication from a foreign patent office in a counterpart foreign application and, to the knowledge of undersigned after making reasonable inquiry, was not known to any individual designated in 1.56(c) more than three months prior to the filing of this IDS.

☐ ii. Please charge Deposit Account 20-1507 for the fee set forth in 1. 17(p), presently believed to be $180 ($90 for Small Entity).

☐ D. after (A), (B) and (C) above, but before payment of the issue fee: Applicant petitions under 37 C.F.R. 1.97(d) for the consideration of this IDS. Under 37 CFR 1.17(p), please charge Deposit Account 20-1507 the fee of $180.00 ($90.00 for Small Entity). Counsel certifies that, upon information and belief, each item of information listed herein was

(check one of the boxes "a" and "b" below:)

☐ (a) 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 this IDS; or

☐ (b) was not cited in a communication from a foreign patent office in a counterpart foreign application and, to the knowledge of undersigned after making reasonable inquiry, was not known to any individual designated in 1.56(c) more than three months prior to the filing of this IDS.

2. In accordance with 37 C.F.R. 1.98, this IDS includes a list (e.g., form PTO/SB/08) of all patents, publications, or other information submitted for consideration by the office, either incorporated into this IDS or as an attachment hereto. A copy of each document listed is attached, except as explained below.

(check boxes A, B and/or C and fill in blanks, if appropriate.)

☒ **A. Pursuant to the Notice issued by the United States Patent and Trademark Office dated July 11, 2003 waiving the requirements of 37 C.F.R. § 1.98(a)(2)(i), a copy/copies of the United States Patent on PTO/SB08 is/are not being submitted.**

☐ B. Document(s) _____is (are) deemed substantially cumulative to document(s) _____ , and, in accordance with 1.98(c), only a copy of each of the latter documents is enclosed.

☐ C. Certain documents were previously cited by or submitted to the Office in the following prior applications, which are relied upon under 35 U.S.C. 120:

<<INSERT SERIAL NO. & FILING DATE>>

Applicant identifies these documents by attaching hereto copies of the forms PTO-892, PTO-1449 and/or PTO/SB/08 from the files of the prior application(s) or a fresh PTO/SB/08 listing these documents, and request that they be considered and made of record in accordance with 1.98(d). Per 37 CFR 1.98(d), copies of these documents need not be filed in this application.

☐ 3. Foreign Patent Document Cite No. ____ is not in the English language. In accordance with 1.98(c), Applicant states:

- ☐ An English translation of each document (or of the pertinent portions thereof), or a copy of each corresponding English-language patent or application, or English-language abstract (or claim) is enclosed.
- ☐ The requirement for a concise explanation of the relevance of any foreign language document is satisfied by the attached search report; citation of the documents cited in the search report shall not be construed as an admission that they are or are considered to be, material to patentability of the subject matter claimed herein (See MPEP §609).
- ☐ A concise explanation of the relevance of document(s) _____ is set forth as follows: [Insert concise explanation of relevance]
- ☐ A concise explanation of the relevance of document(s) _____ can be found on page(s) _____ of the specification.
- ☐ A concise explanation of document(s) _____ can be found on the attached sheet.

[X] **4. No explanation of relevance is necessary for documents in the English language (see reply to Comments 67 in the preamble to the final rules; 1135 OG 13 at 20).**

[X] **5. Other information being provided for the examiner's consideration follows:**

European Search Report dated April 3, 2014, from corresponding European Application Number 14151676.5;

European Search Report dated March 25, 2014, from corresponding European Application Number 14151678.1;

European Search Report dated April 3, 2014, from corresponding European Application Number 14151683.1.

6. In accordance with 37 C.F.R. 1.97(g) and (h), the filing of this IDS should not be construed as a representation that a search has been made or that information cited is, or is considered to be, material to patentability as defined in §1.56 (b), or that any cited document listed or attached is (or constitutes) prior art. Unless other-wise indicated, the date of publication indicated for an item is taken from the face of' the item and Applicant reserves the right to prove that the date of publication is in fact different.

Early and favorable consideration is earnestly solicited.

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

Dated: September 11, 2014

Respectfully submitted,

/Clark G. Sullivan/

Clark G. Sullivan
Registration No.: 36,942
Troutman Sanders LLP
The Chrysler Building
405 Lexington Avenue
New York, New York 10174
Direct Tel: (212) 704-6105
Fax: (212) 704-6288
Direct E-mail:
clark.sullivan@troutmansanders.com
Attorneys/Agents for Applicant

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.
14/069,927	11/01/2013	Fabio TRENTO	244168.000015US4	3207

6980 7590 11/28/2014

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

EXAMINER
WEBB, WALTER E

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
11/28/2014	ELECTRONIC

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

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

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

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

Office Action Summary	Application No. 14/069,927	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 *3/21/2014*.

☐ 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) *52-67* is/are pending in the application.

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

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *52-67* is/are rejected.

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

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

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

Application Papers

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

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

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

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

Priority under 35 U.S.C. § 119

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

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

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

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

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

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

Attachment(s)

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

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date *9/11/2014, 4/29/14*.

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

4) ☐ Other: _____.

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

DETAILED ACTION

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).

Claims 52-67 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 they both claim a method of treating nausea and vomiting (CINV) by administering netupitant and palonesetron.

Conclusion

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

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Walter E. Webb whose telephone number is (571) 270-3287. The examiner can normally be reached on 9:00am-5:00pm Tues-Thurs EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick F. Krass can be reached (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Walter E. Webb
/WALTER WEBB/
Primary Examiner, Art Unit 1612

PTO/SB/08a (01-10)
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	14069927
Filing Date	2013-11-01
First Named Inventor	Fabio TRENTO
Art Unit	1612
Examiner Name	Walter E. WEBB
Attorney Docket Number	244168.000015US4

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
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Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20090036459		2009-02-05	ANDREWS ET AL.	

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	1	2007/096763	WO		2007-08-30	PFIZER LIMITED	Corresponds to US 20090036459	☐

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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /W.W./

Receipt date: 09/11/2014	Application Number	14069927
INFORMATION DISCLOSURE STATEMENT BY APPLICANT	Filing Date	2013-11-01
	First Named Inventor	Fabio TRENTO
(Not for submission under 37 CFR 1.99)	Art Unit	1612
	Examiner Name	Walter E. WEBB
	Attorney Docket Number	244168.000015US4

	1	European Search Report dated April 3, 2014, from corresponding European Application Number 14151676.5.	☐
	2	European Search Report dated March 25, 2014, from corresponding European Application Number 14151678.1.	☐
	3	European Search Report dated April 3, 2014, from corresponding European Application Number 14151683.1.	☐

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EXAMINER SIGNATURE

Examiner Signature	/Walter Webb/	Date Considered	11/21/2014

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BIB DATA SHEET

CONFIRMATION NO. 3207

SERIAL NUMBER	FILING or 371(c) DATE RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
14/069,927	11/01/2013	514	1612	244168.000015US4

APPLICANTS

Helsinn Healthcare S.A., Lugano/Pazzallo, SWITZERLAND, Assignee (with 37 CFR 1.172 Interest);

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 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 ****

11/18/2013

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					
Verified and Acknowledged	/WALTER E WEBB/ Examiner's Signature	Initials	ITALY	5	16	3

ADDRESS

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

TITLE

COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING

FILING FEE RECEIVED		
1740	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

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14069927	TRENTO ET AL.
	Examiner	Art Unit
	WALTER WEBB	1612

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner
514	17.7	11/21/2014	WW

SEARCH NOTES		
Search Notes	Date	Examiner
Inventor Name Search on PALM	11/21/2014	WW
EAST Search History	11/21/2014	WW
NPL Search Terms: netupitant palonosetron	11/21/2014	WW

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

Receipt date: 04/29/2014

Substitute for form 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	14/069,927
				Filing Date	2013-11-01
				First Named Inventor	Fabio TRENTO
				Art Unit	1612
(Use as many sheets as necessary)				Examiner Name	Unassigned
Sheet	1	of	2	Attorney Docket Number	244168.000015US4

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Patent/ Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	A1	5202333	4/13/1993	Berger et al.	
	A2	5510486	4/23/1996	Robinson, III et al.	
	A3	6297375	10/2/2001	Bos et al.	
	A4	6719996	4/13/2004	Kuentz et al.	
	A5	6593472	7/15/2003	Hoffmann et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]
	B1	WO 2008/049552 A 1	2008-05-02	Helsinn Healthcare SA		
	B2	WO 2004/067005 A 1	2004-08-12	Helsinn Healthcare SA		
	B3	WO 2004/073714 A1	2004-09-02	Helsinn Healthcare SA		
	B4	WO 2004/045615 A1	2004-06-03	Helsinn Healthcare SA		

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	C1	Press Release, GSK provides update on regulatory filings for Zunrisa/Rezonic; Issued: Monday 28 September 2009, London UK.	
	C2	WARR et al., Efficacy and tolerability of aprepitant for the prevention of chemotherapy-induced nausea and vomiting in patients with breast cancer after moderately emetogenic chemotherapy. (2005) J. Clin. Oncol. 23(12):2822-2830.	
	C3	HERRINGTON et al., Randomized, placebo-controlled, pilot study evaluating aprepitant single dose plus palonosetron and dexamethasone for the prevention of acute and delayed chemotherapy-induced nausea and vomiting. (2008) Cancer 112(9):2080-2087.	
	C4	YEO et al., A randomized study of aprepitant, ondansetron and dexamethasone for chemotherapy-induced nausea and vomiting in Chinese breast cancer patients receiving moderately emetogenic chemotherapy. (2009) Breast Cancer Res. Treat. 113:529-535.	
	C5	LONGO et al., Palonosetron plus 3-day aprepitant and dexamethasone to prevent nausea and vomiting in patients receiving highly emetogenic chemotherapy. (2011) Support Care Cancer 19:1159-1164.	
	C6	Press Release, NK1 receptor antagonist by Roche; Issued: Thursday, 23 February 2006, http://leaddiscovery.blogspot.com/2006/02/nk1-receptor-antagonist-by-roche.html (leaddiscovery.co.uk)	
	C7	March 27, 2003, Approved FDA Prescribing Information for Emend	

Examiner Signature		Date Considered	

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /W.W./

Substitute for form 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	14/069,927
				Filing Date	2013-11-01
				First Named Inventor	Fabio TRENTO
				Art Unit	1612
(Use as many sheets as necessary)				Examiner Name	Unassigned
Sheet	2	of	2	Attorney Docket Number	244168.000015US4

	C8	RUHLMANN, CHRISTINA et al., "Casopitant: a novel NK1-receptor antagonist in the prevention of chemotherapy- induced nausea and vomiting," Therapeutics and Clinical Risk Management, 2009:5 pp. 375-384	
	C9	PELLEGATTI, MARIO et al., "Disposition and Metabolism of Radiolabeled Casopitant in Humans," Drug Metabolism 0 and Disposition, vol. 37, no. 8, 2009, pp.1635-1645	
	C10	HUANG, SHIH-CHUNG et al., "Neurokinin-1 receptor antagonists: a comprehensive patent survey," Expert Opin. Ther. 0 Patents (2010) 20(8), pp. 1019-1045	
	C11	REDDY, G. KESAVA et al., "Novel Neurokinin-1 Antagonists as Antiemetics for the Treatment of Chemotherapy-Induced Emesis," Supportive Cancer Therapy, April 1, 2006, LNKD-PUBMED: 18632487, vol. 3, no. 3, pp. 140-142, XP002626039, ISSN: 1543-2912	
	C12	DE WIT, R., "Current position of 5HT3 antagonists and the additional value of NK1 antagonists; a new class of antiemetics," British Journal of Cancer, June 16, 2003, LNKD-PUBMED: 12799621, vol. 88, no. 12, pp. 1823-1827, XP002626041, ISSN: 0007-0920	
	C13	DIEMUNSCH, P. et al., "Neurokinin-1 receptor antagonists in the prevention of postoperative nausea and vomiting," British Journal of Anaesthesia, July 2009, LNKD-PUBMED: 19454547, vol. 103, no. 1, pp. 7-13, XP002626040, ISSN: 1471-6771	
	C14	DIEMUNSCH, PIERRE et al., "Potential of Substance P Antagonists as Antiemetics," January 1,2003, Antiemetic Therapy, Basel [U.A.]: Karger, CH, pp. 78-97, XP008133831, ISBN: 978-3-8055-7547-8	
	C15	GRUNBERG, STEVEN M., et al., "Effectiveness of a single-day three-drug regimen of dexamethasone, palonosetron, and aprepitant for the prevention of acute and delayed nausea and vomiting caused by moderately emetogenic chemotherapy," Support Care Cancer: Official Journal of the Multinational Association of Supportive Care in Cancer, May 2009 LNKD-PUBMED: 19037667, vol. 17, no. 5, pp. 589-594, XP002626042, ISSN: 1433-7339	
	C16	STATHIS, MARIGO et al., "Inhibition of substance P-mediated responses in NG1 08-15 celis by netupitant and palonosetron exhibit synergistic effects," European Journal of Pharmacology 689 (2012) pp. 25-30	

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Examiner Signature	/Walter Webb/	Date Considered	11/21/2014

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /W.W./

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	69443	nausea or vomiting or emesis	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2014/11/21 21:33
L2	1694	palonosetron or netupitant	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2014/11/21 21:34
L3	861	l1 and l2	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2014/11/21 21:34
L4	1	l3 and palonesetron	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2014/11/21 21:34
L5	42	l3 and netupitant	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2014/11/21 21:35
L6	846	l3 and palonosetron	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2014/11/21 21:35
L7	27	l5 and l6	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2014/11/21 21:35

11/21/2014 9:37:28 PM
C:\Users\wwebb\Documents\EAST\Workspaces\14069927_Method of treating nausea vomiting with palonosetron and netupitant.wsp

Docket No.: 244168.000015US4
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Fabio Trento et al.	Customer No.: 06980
Application No.: 14/069,927	Confirmation No.: 3207
Filing Date: November 1, 2013	Art Unit: 1612
For: COMPOSISTIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITTING	Examiner: Walter E. Webb

RESPONSE TO INFORMATIONAL NOTICE TO APPLICANT

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

Dear Sir:

In response to the Informational Notice dated April 1, 2014 regarding the present application, Applicant submits executed declarations. The late declaration surcharge was previously submitted, therefore, no fees are believed to be due with this submission.

Dated: December 23, 2014

Respectfully submitted,

/Clark G. Sullivan/

Clark G. Sullivan
Registration No.: 36,942
Troutman Sanders LLP
The Chrysler Building
405 Lexington Avenue
New York, New York 10174
Direct Tel: (212) 704-6105
Fax: (212) 704-6288
Direct E-mail:
clark.sullivan@troutmansanders.com
Attorneys/Agents for Applicant

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

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

As the below named inventor, I hereby declare that:

This declaration is directed to:

☐ The attached application, or

☒ United States application or PCT international application number 14/069,927 filed on 11/01/2013.

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

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

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

WARNING:

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LEGAL NAME OF INVENTOR

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

Signature: Fabio Trento

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

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

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LEGAL NAME OF INVENTOR

Inventor: Sergio Cantarelli Date (Optional): December 12, 2014

Signature: [signature]

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

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LEGAL NAME OF INVENTOR

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

Signature: Giorgia Rossi

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

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PTO/AIA/01 (08-12)
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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

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

As the below named inventor, I hereby declare that:

This declaration is directed to:

- ☐ The attached application, or
- ■ United States application or PCT international application number 14/069,927 filed on 11/01/2013.

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

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

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

WARNING:

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

LEGAL NAME OF INVENTOR

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

Signature: Roberta Cannella

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

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

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

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

As the below named inventor, I hereby declare that:

This declaration is directed to:

☐ The attached application, or

☒ United States application or PCT international application number 14/069,927 filed on 11/01/2013.

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

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

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LEGAL NAME OF INVENTOR

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

Signature: Daniele Bonadeo

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

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

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Electronic Acknowledgement Receipt

EFS ID:	21054644
Application Number:	14069927
International Application Number:	
Confirmation Number:	3207
Title of Invention:	COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING
First Named Inventor/Applicant Name:	Fabio TRENTO
Customer Number:	6980
Filer:	Clark G. Sullivan/Dwight Peck
Filer Authorized By:	Clark G. Sullivan
Attorney Docket Number:	244168.000015US4
Receipt Date:	23-DEC-2014
Filing Date:	01-NOV-2013
Time Stamp:	16:49:12
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Miscellaneous Incoming Letter	PTO-SubmissionofDecTrans-US4.PDF	55420 5d0448256efdb43e0e9122bdb0e6e017232c6b2b	no	1

Warnings:	
Information:	

2	Oath or Declaration filed	PTO-Declarations-US4.PDF	228447 d1e9f09c4c5e19106e12bd92abace6547edbc7bd	no	5

Warnings:	
Information:	
Total Files Size (in bytes):	283867

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

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

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

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	14069927
Filing Date	2013-11-01
First Named Inventor	Fabio TRENTO
Art Unit	1612
Examiner Name	Walter E. WEBB
Attorney Docket Number	244168.000015US4

U.S.PATENTS

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Patent citation information please click the Add button.

U.S.PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	2009-507933	JP		2009-02-26	Helsinn Healthcare S.A.	Corresponds to WO 2008049552 (previously cited).	☒

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]

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14069927
	Filing Date	2013-11-01
	First Named Inventor	Fabio TRENTO
	Art Unit	1612
	Examiner Name	Walter E. WEBB
	Attorney Docket Number	244168.000015US4

	1	Japanese Office Action dated November 19, 2014, which issued during prosecution of Japanese Patent Application No. 2012-539433.	☒
	2	Torsten HOFFMANN, et al., "Design and synthesis of a novel, achiral class of highly potent and selective, orally active neurokinin-1 receoptor antagonists", Bioorganic & Medicinal Chemistry Letters 16 (2006) 1362-1365.	☐

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	14069927
	Filing Date	2013-11-01
	First Named Inventor	Fabio TRENTO
	Art Unit	1612
	Examiner Name	Walter E. WEBB
	Attorney Docket Number	244168.000015US4

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)	2015-01-15
Name/Print	Clark Sullivan	Registration Number	36,942

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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 the Freedom of Information Act requires disclosure of these record s.

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

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

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

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

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

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

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

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

Espacenet

Bibliographic data: JP2009507933 (A) — 2009-02-26

SOFT CAPSULES COMPRISING PALONOSETRON HYDROCHLORIDE HAVING IMPROVED STABILITY AND BIOAVAILABILITY

Inventor(s):

Applicant(s):

Classification: **- international:** *A61K31/439; A61K47/10; A61K47/14; A61K47/36; A61K47/38; A61K47/42; A61K9/48; A61P1/08*
- cooperative: A61K31/473; A61K9/4858

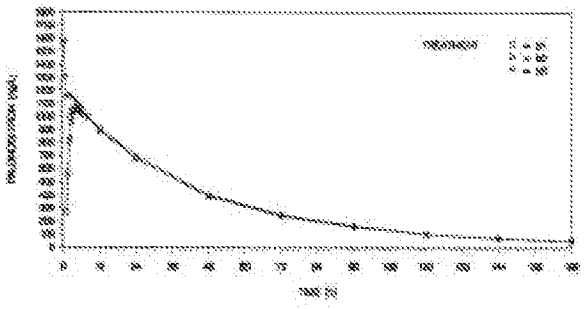
Application number: JP20080540633 20071019

Priority number (s): US20060854342P 20061024 ; WO2007EP09098 20071019

Also published as: JP5144527 (B2) WO2008049552 (A1) ZA200902773 (A) US2008152704 (A1) TW200827355 (A) more

Abstract not available for JP2009507933 (A)
Abstract of corresponding document: WO2008049552 (A1)

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.



(19)日本国特許庁(JP)　(12)公表特許公報(A)　(11)特許出願公表番号
特表2009-507933
(P2009-507933A)
(43)公表日　平成21年2月26日(2009.2.26)

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A61K 31/439	(2006.01)	A61K	31/439	4C076
A61K 9/48	(2006.01)	A61K	9/48	4C086
A61K 47/42	(2006.01)	A61K	47/42	
A61K 47/10	(2006.01)	A61K	47/10	
A61K 47/38	(2006.01)	A61K	47/38	

審査請求 有　予備審査請求 未請求　（全 29 頁）　最終頁に続く

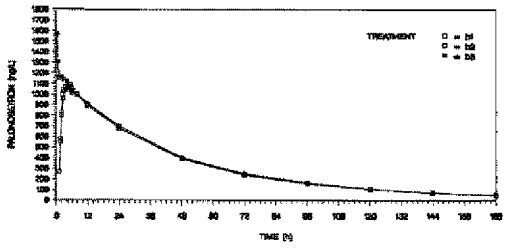
(21)出願番号　特願2008-540633 (P2008-540633)
(86)(22)出願日　平成19年10月19日 (2007.10.19)
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(87)国際公開番号　WO2008/049552
(87)国際公開日　平成20年5月2日 (2008.5.2)
(31)優先権主張番号　60/854,342
(32)優先日　平成18年10月24日 (2006.10.24)
(33)優先権主張国　米国 (US)

(71)出願人　505180070
ヘルシン　ヘルスケア　ソシエテ　アノニム
スイス国，チアッカ－６９１５　ルガーノ，パムビオ－ノランコ，ピ．オ．ボックス　３５７
(74)代理人　100099759
弁理士　青木　篤
(74)代理人　100077517
弁理士　石田　敬
(74)代理人　100087871
弁理士　福本　積
(74)代理人　100087413
弁理士　古賀　哲次

最終頁に続く

(54)【発明の名称】改良された安定性と生物学的利用能をもつ塩酸パロノセトロンの投与形態

(57)【要約】
塩酸パロノセトロンの固体経口投与形態、当該投与形態を用いて吐き気を治療する方法、及び当該投与形態の製造方法を提供する。本投与形態は、改善された安定性と生物学的利用能を有し、そして好ましくは液体充填カプセルの形態にある。



【特許請求の範囲】
【請求項1】
経口投与のためのソフトゼラチンカプセルであって、以下の：
ａ）約１．０×１０$^{-3}$ｍｌ・ｃｍ／（ｃｍ^{2}・２４時間ａｔｍ）未満の酸素透過性を有するソフトゼラチン外部シェル；並びに
ｂ）親油性液体内部充填組成物であって以下の：
ｉ）約５０ｗｔ％超の１以上の親油性成分；
ii）上記１以上の親油性成分中に混和され又は均質化された約１～約２０ｗｔ％の水；
iii）上記水中に溶解され又は分散された、塩酸パロノセトロンとしての約０．５～約２．０ｍｇのパロノセトロン；及び
iv）界面活性剤；
を含むもの；
を含み、ここで、前記カプセルは、絶食状態において経口摂取されるとき９５％超の絶対生物学的利用能をもつ配合品に生物学的に等価である薬物動態を示し、ここで、当該生物学的等価性は、８０％～１２５％の間のＡＵＣについて９０％の信頼区間により確立される、前記カプセル。
【請求項2】
前記内部充填組成物が、以下の：
ａ）塩酸パロノセトロンとしての０．５～１．０ｍｇのパロノセトロン；及び
ｂ）親油性賦形剤と水を含む、可溶化有効量の水；
を含む、請求項１に記載のカプセル。
【請求項3】
前記外部シェルと前記内部充填組成物内にグリセリンを含む、請求項１に記載のソフトゼラチンカプセル。
【請求項4】
ａ）前記内部充填組成物が、抗酸化剤又は還元剤をさらに含み；
ｂ）前記パロノセトロンが、約１ｗｔ％未満のＣｄｐ１を含む、
請求項１に記載のソフトゼラチンカプセル。
【請求項5】
絶食状態において経口摂取されるとき、９５％超の絶対生物学的利用能を有する配合品に生物学的に等価である薬物動態、及び８００～８２０ｎｇ／ＬのC$_{max}$を示し、ここで、当該生物学的等価性は、以下の：
ａ）８０％～１２５％の間にあるＡＵＣについての９０％信頼区間、及び
ｂ）８０％～１２５％の間にあるC$_{max}$についての９０％信頼区間、
により確立される、請求項１に記載のソフトゼラチンカプセル。
【請求項6】
前記内部充填組成物が、前記投与形態が４０℃及び７５％ＲＨで３ヶ月間保存されるとき、約３．０ｗｔ％以下の酸化的分解を仲介する量の酸素を含む、請求項１に記載のカプセル。
【請求項7】
５００ｍｌの０．０１Ｎ　ＨＣｌ中７５ｒｐｍ及び３７℃で、米国薬局方に従うタイプIIパドル溶解装置内で試験されるとき、前記パロノセトロン又は医薬として許容されるその塩の約７５％以上が、４５分で溶解する、請求項１に記載のカプセル。
【請求項8】
５００ｍｌの０．０１Ｎ　ＨＣｌ中７５ｒｐｍ及び３７℃で、米国薬局方に従うタイプIIパドル溶解装置内で試験されるとき、前記パロノセトロン又は医薬として許容されるその塩の約７５％以上が、３０分で溶解する、請求項１に記載のカプセル。
【請求項9】

前記シェルが、約１．０×１０$^{-4}$ｍｌ・ｃｍ／（ｃｍ^{2}・２４時間・ａｔｍ）未満の酸素透過性を有する、請求項１に記載のカプセル。

【請求項10】

前記内部充填物が、０．５～４ｗｔ％の界面活性剤を含む、請求項１に記載のカプセル。

【請求項11】

経口投与のための液体充填ソフトカプセル投与形態であって、以下の：

ａ）約１．０×１０$^{-3}$ｍｌ・ｃｍ／（ｃｍ^{2}・２４時間・ａｔｍ）未満の酸素透過性を有する外部シェル；及び

ｂ）約０．０５～約２．０ｍｇのハロノセトロン又は医薬として許容されるその塩を含む内部充填組成物、ここで当該パロノセトロン又は医薬として許容されるその塩は、当該パロノセトロンの重量に基づき、１．０ｗｔ％未満の量のＣｐｄ１又は医薬として許容されるその塩を含む；

を含み、ここで、前記内部充填組成物は、当該投与形態が４０℃及び７５％ＲＨで３ヶ月間以上の間保存されるとき当該パロノセトロン又は医薬として許容されるその塩の約３．０ｗｔ％以下の酸化的分解を仲介する量の酸素を含む前記投与形態。

【請求項12】

絶食状態において経口摂取されるとき、９０％超の絶対生物学的利用能を有する配合品に生物学的に等価な薬物動態を示し、ここで、当該生物学的等価性は、８０％～１２５％の間のＡＵＣについて９０％信頼区間に確立される、請求項１１に記載のカプセル。

【請求項13】

前記内部充填組成物が、約１ｗｔ％～約２０ｗｔ％の水を含む、請求項１１に記載のカプセル。

【請求項14】

絶食状態において経口摂取されるとき９５％超の絶対生物学的利用能を有する配合品に生物学的に等価である薬物動態、及び８００～８２０ｎｇ／ＬのＣ$_{max}$を示し、ここで当該生物学的等価性は、以下の：

ａ）８０％～１２５％の間ＡＵＣについての９０％信頼区間；及び

ｂ）８０％～１２５％の間にあるＣ$_{max}$についての９０％信頼区間；

により確立される、請求項１１に記載のカプセル。

【請求項15】

５００ｍｌの０．０１Ｎ　ＨＣｌ中７５ｒｐｍ及び３７℃で、米国薬局方に従うタイプIIパドル溶解装置内で試験されるとき、前記パロノセトロン又は医薬として許容されるその塩の約７５％以上が、４５分で溶解する、請求項１１に記載のカプセル。

【請求項16】

前記シェルが、約１．０×１０$^{-4}$ｍｌ・ｃｍ／（ｃｍ^{2}・２４時間・ａｔｍ）未満の酸素透過性を有する、請求項１１に記載のカプセル。

【請求項17】

ａ）前記内部充填組成物がグリセリンを含み；そして

ｂ）前記シェルがグリセリンを含む；

請求項１１に記載のカプセル。

【請求項18】

前記シェルは、ゼラチン、セルロース、デンプン又はＨＰＭＣを含む、請求項１１に記載のカプセル。

【請求項19】

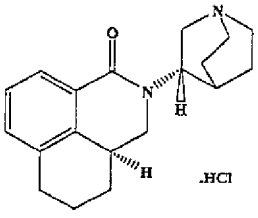
パロノセトロンゼラチンカプセル内のパロノセトロンの生物学的利用能及び安定性を最適化する方法であって、以下のステップ：

ａ）約１．０×１０$^{-3}$ｍｌ・ｃｍ／（ｃｍ^{2}・２４時間・ａｔｍ）未満の酸素透過性を有するソフトゼラチンカプセルを提供し；そして

ｂ）以下のステップ：

ｉ）塩酸パロノセトロンとして約０．０５～約２．０ｍｇのパロノセトロンを提供し、ここで当該パロノセトロンは、３．０ｗｔ％未満の量のＣｐｄ１を含む；
ii）水に前記パロノセトロンを溶解又は分散させて、水性プレミックスを形成し；
iii）前記水性プレミックスを１以上の親油性賦形剤と、水性プレミックス対親油性賦形剤３０未満：７０の重量比で、混合して、混和性又は均質の親油性充填組成物を形成し；
iv）界面活性剤を、前記水、前記水性プレミックス、又は前記充填組成物と、混合し；そして
ｖ）前記充填組成物中の界面活性剤の量と水の量をバランスさせて、経口摂取されたときの前記ゼラチンカプセルからのパロノセトロンの生物学的利用能を促進させ、かつ、パロノセトロンの分解の程度を最小化する；そして
ｃ）前記外部シェルに前記充填組成物を充填する；
を含む前記方法。
【請求項20】
前記充填組成物が、約０．１～約１０．０ｗｔ％の界面活性剤、及び約０．１～２０ｗｔ％の水を含む、請求項１９に記載の方法。
【請求項21】
前記充填組成物が、約０．５～約４ｗｔ％の界面活性剤、及び約１～約１０ｗｔ％の水を含む、請求項１９に記載の方法。
【請求項22】
前記外部シェルがグリセリンをさらに含み、そして前記新油性充填組成物を形成する前又は後に、前記水性プレミックスをグリセリンと混合することをさらに含む、請求項１９に記載の方法。
【請求項23】
不純物の量及び酸素仲介分解が低減されたパロノセトロンの投与形態のバッチの製造方法であって、以下のステップ：
ａ）塩酸パロノセトロンと１以上の医薬として許容される賦形剤を混合して、混合物を形成し；
ｂ）前記混合物を、複数の最終投与形態まで加工し；そして
ｃ）Ｃｐｄ１、Ｃｐｄ２及びＣｐｄ３から選ばれる１以上のパロノセトロン関連化合物、又はそれらの塩酸塩について、前記最終投与形態の内の１以上を試験する；
を含む前記方法。
【請求項24】
Ｃｐｄ１又はその塩酸塩について試験することを含む、請求項２３に記載の方法。
【請求項25】
Ｃｐｄ２又はその塩酸塩について試験することを含む、請求項２３に記載の方法。
【請求項26】
Ｃｐｄ３又はその塩酸塩について試験することを含む、請求項２３に記載の方法。
【請求項27】
Ｃｐｄ４，Ｃｐｄ５，Ｃｐｄ６、又はＣｐｄ７から選ばれる１以上の化合物又はその塩酸塩について、前記塩酸パロノセトロン又は前記最終投与形態を試験することをさらに含む、請求項２３に記載の方法。
【発明の詳細な説明】
【技術分野】
【0001】
先の出願との関係
本発明は、２００６年１０月２４日に出願された米国仮出願第６０／８５４，３４２号（失効）に基づく優先権を主張する。
本発明の分野
本発明に、保存安定性要求を満たす、パロノセトロン（palonosetron）、及び特にパロノセトロンの固体経口投与形態（剤形）に関する。

【背景技術】
【0002】
本発明の背景
抗癌化学療法及び放射線療法の吐き気（nausea and emetogenic）副作用は、広くかつ長く続く問題である。おそらくあまりよく知られていないが重要な問題は、術後の吐き気であり、これは、化学療法に関して見られる効果に関連する生理学的メカニズムをもちうる。塩酸パロノセトロン（palonosetron hydrochloride）は、吐き気誘発性抗癌化学療法とともに使用される高く有効な抗吐き気薬として最近出現した（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）。パロノセトロンは、術後の吐き気をも防止する（Chelly, J. et al. , “Oral RS-25259 Prevents postoperative nausea and vomiting following laparoscopic surgery, ”Anesthesiol. , 85（Suppl. 21）：abstract no. 3A（1996））。パロノセトロンにより、化学療法誘導吐き気（Chemotherapy induced nausea and vomiting（ＣＩＮＶ））及び放射線誘導吐き気（radiation induced nausea and vomiting（ＲＩＮＶ））を治療する方法は、Helsinn Healthcare SAからのＰＣＴ公開ＷＯ２００４／０４５６１５号中に記載されている。パロノセトロンによる術後吐き気（post-operative nausea and vomiting（ＰＯＮＶ））もHelsinn Healthcare SAからのＰＣＴ公開ＷＯ２００４／０７３７１４号中に記載されている。
【0003】
パロノセトロンは、選択的であり、５－ヒドロキシルトリプタミン３受容体前駆体（５－HT_3受容体）のアンタゴニストとして高いアフィニティーを示し、かつ、他の受容体、例えば、ドーパミン受容体について低いアフィニティーを示す（Wong, E. H. F. , et al. , “The interaction of RS 25259-197, a potent and selective antagonist, with 5-HT_3 receptors, in vitro, ”Br. J. Pharmacol. , 114：851-859（1995）；Eglen, R. M. , et al. , “Pharmacological characterization of RS 25259-197, a potent and selective antagonist, with 5-HT_3 receptors, in vivo, ”Br. J. Pharmacol. , 114：860-866（1995））。
【0004】
パロノセトロンは、単一の異性体とに存在する合成化合物であり、以下の構造：
【化1】



で表されるような、塩酸塩として投与される。
【0005】
この医薬の正式な化学名は、（３ａＳ）－２－［（Ｓ）－１－アザビシクロ［２．２．２］オクト－３－イル］－２，３，３ａ、４，５，６－ヘキサヒドロ－１－オキソ－１Ｈベンズ［ｄｅ］イソキノリンヒドロクロリド（ＣＡＳ　Ｎｏ．１９９０４－９０－４）であり；その実験式は$C_{19}H_{24}N_2O$・ＨＣｌであり、そしてその分子量は３３２．８７である。当該化合物の合成方法は、米国特許第５，２０２，３３３号及び同第５，５１０，４８６号中に記載されている。
【0006】

塩酸パロノセトロンは、ＭＧＩ　Pharma　及びHelsinn Healthcare SAによりＡＬＯＸＩ（登録商標）として米国内で滅菌注射液として販売されている。静中液は、等張緩衛溶液中、透明、無職、非発熱性である。注射用のパロノセトロンの安定等張溶液は、HelsinnのＰＣＴ公開ＷＯ２００４／０６７００５号中に記載されている。

【0007】

上記静脈中製剤の多くの臨床的利益及び利点にも拘らず、注射ドラッグデリバリーシステムは活性剤の保存寿命及び安定性に関して特別な問題を提示すると一般に認められる。それらは、自己投与され、そして汚染及びヒューマンエラーの高められたリスクをもつとき、不便でもある。したがって、特に固体形態にある、パロノセトロンのための経口デリバリー・オプションは、特に魅力的であろう。パロノセトロン配合品の安定性及び保存寿命を改善する方法も所望される。

【発明の開示】

【0008】

本発明の概要

パロノセトロンのソフトゲルカプセルであって、経口投与されるとき優れた生物学的利用能を示し、そして長期間保存されるとき優れた安定性を示すものが今般開発された。カプセルの外部シェルはゼラチンベースであり、そしてカプセルの内部充填物は、最小量の界面活性剤により親油性相中に混和され又は均質化された水性成分中に溶解されたパロノセトロンを含有する連続親和性内相である。配合品は、以下の：

・水性充填物とゼラチン安定性；

・界面活性剤とパロノセトロン分解；及び

・パロノセトロン安定性とパロノセトロン濃度；

の間に一般に観察される緊張状態に対して優れた溶液を提示する。

【0009】

それゆえ、第１の主な態様においては、本発明は、経口投与のためのソフトゼラチンカプセルであって、以下の：

（ａ）約１．０×１０$^{-3}$ｍｌ・ｃｍ／（ｃｍ^2・２４時間・ａｔｍ）未満の酸素透過性を有するソフトゼラチン外部シェル；並びに

（ｂ）親油性液体内部充填組成物であって、以下の：

ｉ）約５０ｗｔ％超の１以上の親油性成分；

ii）約１～約２０ｗｔ％の、上記１以上の親油性成分中に混和され又は均質化された水；

iii）約０．０５～約２．０ｍｇの、上記水中に溶解され又は分散された塩酸パロノセトロンとしてのパロノセトロン；及び

iv）約０．５～約５ｗｔ％の界面活性剤；

を含むもの；

を含むソフトゼラチンカプセルを提供する。

【0010】

配合及び製造方法であって、投与形態内のパロノセトロンの量又は濃度、及び投与形態内の分解副産物により規定されるものも開発された。このような１の分解副産物は、酸素仲介分解産物であり、そして本明細書中“Ｃｐｄ１”という。

【0011】

その製造方法を含む、パロノセトロンの投与形態であって、酸素及び酸素仲介分解からのそれらの保護に因り高められた安定性をもつものも、開発された。これらの発見及び開発に基づき、以下の物理的特徴の内の１以上により規定されうる投与形態が開発された：

・酸素に対し実質的に不透過性であるシェル又はコーティング；

・カプセルシェル内の、好ましくは水を含有する充填液体充填物の使用；

・上記液体充填物中の最小酸素含有量；

・酸化的分解を防止するための化学的手段；

・酸素透過に対して抵抗性である水分耐性パッケージング；及び／又は

・投与形態製造時の酸素低下環境の使用。

【0012】

これらの投与形態は、長期間にわたる優れた安定性、酸化的分解に対する優れた抵抗性、及び経口摂取時の優れた生物学的利用能を有する。これらの投与形態は、パロノセトロンが臨床上の用途をもつところのいずれかの疾患の治療のために使用されうるが、それらは好ましくは、吐き気の治療のために使用される。

【0013】

それゆえ、第２の主な態様においては、本発明は、経口投与のためのカプセル投与形態であって、以下の：

（ａ）約１．０×１０$^{-3}$ｍｌ・ｃｍ／（ｃｍ^{2}・２４時間・ａｔｍ）未満の酸素透過性を有する外部シェル；並びに

（ｂ）内部充填組成物であって、塩酸パロノセトロンとして約０．０５～約２．０ｍｇのパロノセトロンを含むもの；

を含み、ここで上記パロノセトロンは、１．０ｗｔ％未満の量のＣｐｄ１を含み；

ここで、上記投与形態が３ヶ月間又は４０℃及び７５％ＲＨで保存されるとき、上記パロノセトロンの５．０ｗｔ％以下が分解される、前記カプセル投与形態を、提供する。

【0014】

もちろん、本発明は、カプセル以外の投与形態を用いて実施されることができ、そして他の態様においては、本発明は、固体経口投与形態であって、以下の：

（ａ）約１．０×１０$^{-3}$ｍｌ・ｃｍ／（ｃｍ^{2}・２４時間・ａｔｍ）未満の酸素透過性を有する外側シェル又はコーティング；並びに

（ｂ）塩酸パロノセトロンとして約０．０５～約２．０ｍｇのパロノセトロンを含む内部充填組成物；

を含み、ここで、上記パロノセトロンは、１．０ｗｔ％未満の量のＣｐｄ１を含み；

ここで、上記投与形態が３ヶ月以上４０℃及び７５％ＲＨで保存されるとき、上記塩酸パロノセトロンの５．０ｗｔ％以下が分解される、前記固体経口投与形態を、提供する。

【0015】

不純物及び酸素仲介分解産物の量が低下されたパロノセトロン投与形態の製造方法、及びこれらの方法により製造されたパロノセトロンの投与形態も今般開発した。したがって、さらに他の態様においては、本発明は、不純物及び酸素仲介分解産物の量が低下されたパロノセトロンのバッチの製造方法であって、以下のステップ：

（ａ）塩酸パロノセトロンと１以上の医薬として許容される賦形剤を混合して、混合物の形成し；

（ｂ）上記混合物を処理して、複数の最終投与形態にもっていき、そして

（ｃ）Ｃｐｄ１について上記最終投与形態の内の１以上を試験する；

を含む前記方法を提供する。この方法は、カプセル、ゲルキャップ又は液体充填アンプルを含む、いずれかの投与形態とともに実施されうる。

【0016】

本発明の追加の利点は、以下の説明において一部言及し、そして一部は当該説明から自明であろうし、又は本発明の実施により学習されうる。本発明の利点は、添付のクレームに特に指摘する要素及び組合せにより具現化され、そして達成されるであろう。これらの一般的な説明及び以下の詳細な説明の両者が例示及び説明のみを目的としたものであり、請求されるような、本発明を制限するものではないと理解されよう。

【発明を実施するための最良の形態】

【0017】

本発明は、本発明の好ましい態様の以下の詳細な説明及びその中に含まれる実施例を参照することにより、より容易に理解されうる。

【0018】

定義及び用語の使用

本明細書中及び添付のクレーム中で使用するとき、単数形「ａ」，「ａｎ」、及び「ｔ

ｈｅ」は、別段の定めなき限り、複数指示物を含む。したがって、例えば、「an ingredient（成分）」は、成分の混合物を含み、「an active pharmaceutical agent（活性医薬剤）」は、２以上の活性医薬剤を含む、等である。

【0019】

疾患の「治療（treating or treatment）」は、（１）疾患の素因があるがその疾患のを未だ経験していないかその兆候を示していない動物において、その疾患が生じることを防止すること、（２）その疾患を抑制し、すなわちその発達を休止させること、又は（３）その疾患を緩和し、すなわちその疾患の退縮を引き起すことを含む。

【0020】

本明細書中に使用するとき、周囲環境とは、要素又はプロセスをじかに取り囲む環境、典型的には、要素又はプロセスがそれに接し、そしてそれと連絡するところの気体環境をいう。

【0021】

本発明の目的としての「吐き気（emesis）」は、通常の、辞書の定義よりも広い意味をもち、そして嘔吐だけでなく、吐き気及び吐き気を催すことを含む。

【0022】

「中程度に吐き気を引き起こす化学療法」とは、吐き気の潜在的能力が、カルボプラチン、シスプラチン≦５０ｍｇ／ｍ^2、シクロホスファミド＜１５００ｍｇ／ｍ^2、ドキソルビシン＞２５ｍｇ／ｍｓ、エピルビシン、イリノテカン、又はメトトレキセート＞２５０ｍｇ／ｍ^{2}の吐き気能力に匹敵するか又は等価であるところの化学療法をいう。

【0023】

「高い吐き気を引き起こす化学療法」とは、その吐き気の潜在能力がシスプラチン≧６０ｍｇ／ｍ^2、シクロホスファミド＞１５００ｍｇ／ｍ^2、又はダカルバジンの吐き気能力に匹敵するか又は等価であるところの化学療法をいう。

【0024】

「医薬として許容される」とは、一般に安全であり、非毒性であり、そして生物学的にもその他の点でも不所望ではない医薬組成物の調製に有用であるものを意味し、そして獣医用途並びにヒトの医薬用途に許容されるものを含む。

【0025】

「治療的有効量」とは、疾患を治療するために動物に投与されるとき、当該疾患の治療を行うために十分な量を意味する。

【0026】

「最小」量の酸素とは、６，１２，１８，２４，３０又は３６ヶ月間周囲条件下室温で保存されるとき、パロノセトロンの約０．５，１．０，１．５，２．０，２．５又は３．０ｗｔ％以下が分解される（好ましくはＣｐｄ１への分解により規定される）ことを可能にする酸素の量をいう。

【0027】

本発明の目的としての「保存安定性」は、３，６，１２，１８，２４，３０又は３６ヶ月間、４０℃，７５％の相対湿度で、又は周囲条件下で、そのパッケージング内で投与形態を保存することにより計測される。安定性配合品は、投与形態内のパロノセトロンの約０．５，１．０，１．５，２．０，２．５，３．０、又は５．０ｗｔ％以下が分解される（好ましくは、本明細書中に記載する分解産物の内の１以上の分解により規定される）ところのものをいう。

【0028】

範囲が、その範囲の上限（端）とは別個に範囲の下限を特定することにより与えられるとき、その範囲は、数学的に可能である上限変数の内のいずれか１つと、下限変数の内のいずれか１つを選択的に組み合せることにより規定されうると理解されよう。

【0029】

本明細書中に使用するとき、「約（about）又は（ca．）」は、製薬産業において許容され、そして医薬製品において固有であるバラツキを、例えば、製造上のバラツキ及び時

間誘導製品分解に因る製品強度の差を補償するである。この用語は、医薬の実務において、評価される製品が、請求に係る製品の記載された強度と生物学的に等価であると考えられることを許容するいずれかのバラツキを許容する。

【0030】

用語「絶対生物学的利用能（absolute bioavailability）」とは、非静脈内投与後（すなわち、経口、直腸、経皮、皮下の投与後）全身循環内での活性薬物の利用可能性をいう。医薬の絶対生物学的利用能を測定するためには、静脈内（ＩＶ）と非静脈内投与の両者の後に、当該医薬について、血漿医薬濃度対時間プロットを得るための医薬動態試験を行わなければならない。絶対生物学的利用能は、投与量補正された曲線下面積（ＡＵＣ）非静脈内を、ＡＵＣ静脈内で、割ったものである。配合品は、参照配合品の生物学的利用能の程度に対して、８０％～１２５％の間にあるＡＵＣ（０→∞）について９０％の信頼区間が確立されるとき、当該参照配合品に対して、絶対生物学的利用能に関して、生物学的に等価であるといわれる。

【0031】

薬物動態パラメーター（すなわち、T_{max}絶対生物学的利用能など）を本明細書中に与えるとき、それらは、平均、メジアン、又は個々の観察された薬物動態を指すことができること、そして別段の定めなき限り請求されるとき、その平均薬物動態が意図されることが理解されよう。

【0032】

討議

前記したように、本発明は、酸素に対して実質的に非透過性であるコーティング又はシェルの使用、又はその中に均質化又は混和された水をもつ親油性液体充填物の使用を含む、いくつかの配合技術に基づく、改善された安定性及び酸化的分解に対する抵抗性をもつ固体傾向投与形態を提供する。第１の主な態様においては、本発明は、固体経口投与形態であって、以下の：

（ａ）約１．０×１０$^{-3}$ｍｌ・ｃｍ／（ｃｍ^2・２４時間・ａｔｍ）未満の酸素透過性をもつ外部シェル又はコーティング；並びに

（ｂ）塩酸パロノセトロンとして約０．０５～約２．０ｍｇのパロノセトロンを含む内部充填組成物；

を含み；ここで、上記投与形態は、その投与形態が３ヶ月以上４０℃７５％ＲＨで保存されるとき当該塩酸パロノセトロンの５．０ｗｔ％以下が分解されるように好ましくは規定される、保存安定性を示す。本発明は、さらに、吐き気を患い又は吐き気を患うリスクのある患者に、本発明の投与形態を経口投与することを含む吐き気の治療方法を提供する。

【0033】

本発明は、例えば、カプセル又はゲルキャップ（すなわち、液体充填カプセル）を含む、経口経路を介して投与され又は飲み込まれるいずれかの投与形態として規定される、固体経口投与形態のいずれかのタイプとともに実施されうる。好ましい態様においては、投与形態はカプセルであり、そしてさらにより好ましい態様においては、投与形態は、液体が充填されたゲルキャップ（gel-cap）である。

【0034】

いずれの投与形態であっても、それは、好ましくは、最小の酸素透過性を有する外部シェル又はコーティングをもつ。本発明の好ましい態様においては、コーティング又はシェルは、約１．０×１０$^{-3}$，５．０×１０$^{-4}$，１．０×１０$^{-4}$，５．０×１０$^{-5}$、又はさらに２．０×１０$^{-5}$ｍｌ・ｃｍ／（ｃｍ^2・２４時間・ａｔｍ）未満である酸素透過性を有する。

【0035】

本発明にとっての好ましい投与形態は、胃液中で溶解する外部シェルをもつカプセルである。好ましくは水を含む、液体充填カプセルは、液体とともに働くときの含有量及び投与量の均一性、投与形態の製造及び長期間にわたる投与形態の保存時における酸素露出を

最小化するその能力のために、特に好ましい。

【0036】

利用可能な外部シェルの中で、ソフト外部シェルは、液体を保持し、その酸素透過に抵抗するその能力のために、好ましいシェル構造である。外部「ゲルキャップ」のための好ましい材料は、例えば、ゼラチン、セルロール、デンプン、又はＨＰＭＣを含む。好ましい態様においては、シェルは、ゼラチン、並びに場合により、グリセリン、ソルビトール、及び２酸化チタンから選ばれる１以上のシェル賦形剤を含む。

【0037】

カプセルを満たす液体組成物は、好ましくは、（１）主に親油性であり、そして（２）連続液相として存在する（すなわち、液体成分が混和されているか又は完全化均質化／乳化されている）。連続相は、処理容易性と組成物の均質性のために好ましい。液体充填物は、賦形剤ベースと、その液体充填物の全体にわたり均質に分配された活性剤を含む。さらに、活性剤は、好ましくは、賦形剤ベース中に溶解され又はマイクロエマルジョンとして分散される。充填組成物の総重量は、好ましくは、約５０，７５、又は１００ｍｇ超であり、そして好ましくは約５００，２５０，２００、又は１５０ｍｇ未満であり、より好ましくは、約１００～約１５０ｍｇである。

【0038】

液体充填物は、好ましくは、約５０ｗｔ％～約９０ｗｔ％の、好ましくは約７５ｗｔ％～約９８ｗｔ％の量の１以上の親油性成分から主に構成される。好ましい親油性成分は、例えば、脂肪酸のモノ－及びジ－グリセリドであり、特にカプリル／カプリン酸のモノ－及びジ－グリセリドを含む。液体充填物は、好ましくは約１～約１５ｗｔ％の、より好ましくは約２～約１０ｗｔ％の量のグリセリンを含みうる。１の好ましい態様においては、シェルと内部充填組成物の両者がグリセリンを含む。他の好ましい態様においては、液体充填物は、親油性賦形剤と水を含む、可溶化有効量の液体中に溶解された；塩酸パロノセトロン（すなわち、０．５０又は０．７５ｍｇ）としての０．２５，０．３５ｍｇ以上のパロノセトロンを含む。

【0039】

充填組成物は、パロノセトロンが血流中により容易に吸収されることができるように、投与形態からＧＩ管の胃腸液へのパロノセトロンの移動を容易にするためのさまざまな手段を含みうる。例えば、液体充填組成物は、最適には、約０．１ｗｔ％～約６ｗｔ％の、約０．５ｗｔ％～約５ｗｔ％の、又は約１．０ｗｔ％～約３．０ｗｔ％の量の、界面活性剤を含みうる。液体充填組成物は、好ましくは、０．１，０．５又は１．０ｗｔ％超の界面活性剤、及び１０，８，５，４、又はさらに４ｗｔ％未満の界面活性剤を含む。特に好ましい界面活性剤は、オレイン酸ポリグリセリルである。

【0040】

あるいは又はさらに、液体充填カプセルの移動手段は、単一相、又は賦形剤ベース中の他の液体成分とマイクロエマルジョンを形成する水を含みうる。液体充填組成物は、好ましくは、約０．０５ｗｔ％～約３０ｗｔ％の水、約１ｗｔ％～約２０ｗｔ％の水、又は約２ｗｔ％～約１０ｗｔ％の水を含む。液体充填物は、好ましくは、０．１，０．５又は１．０ｗｔ％超の水、そして２０，１５，１０，８又は５ｗｔ％未満の水を含む。

【0041】

そしてさらに、賦形剤ベースは、投与形態中のパロノセトロンの酸素仲介分解を防止するための１以上の化学作用物質を含みうる。例えば、賦形剤ベースは、約０．００５ｗｔ％～約２．０ｗｔ％の、より好ましくは約０．０１ｗｔ％～約１．０ｗｔ％の、又は約０．０５ｗｔ％～約０．５ｗｔ％の範囲の量の、キレート化剤、例えばエチレンジアミン四酢酸（ＥＤＴＡ）、抗酸化剤、例えばブチル化ヒドロキシルアニソール（ＢＨＡ）、又は還元剤を含みうる。好ましい態様においては、賦形剤ベースは抗酸化剤を含む。

【0042】

好ましくは塩酸パロノセトロンである活性剤は、好ましくは、約０．０１～約１０．０ｗｔ％の、約０．０５～約５．０ｗｔ％の、又は約０．１ｗｔ％～約２．０ｗｔ％の範囲

の量で、充填組成物中に存在する。あるいは、特に安定な配合品は、パロノセトロンの濃度が０．３％を超え、好ましくは、約１ｗｔ％以下の濃度にあるときに、見られる。

【0043】

本発明の態様の内のいずれかにおいて好ましい、内部充填組成物の特に重要な特徴は、投与形態又は充填物のタイプ又は製造方法に拘らず、最小含有量の酸素である。好ましい態様においては、内部充填組成物は、投与形態が、保存安定性試験管理下、例えば３ヶ月間４０℃７５％ＲＨで保存されるとき、当該パロノセトロンの約３．０ｗｔ％，２．５ｗｔ％，２．０ｗｔ％，１．５ｗｔ％，１．０ｗｔ％、又は０．５ｗｔ％以下を分解する量の酸素を含む。この量は、好ましくは、組成物中のＣｐｄ１の量により計測される。

【0044】

本発明に係る配合品の他の重要な特徴は、これらの薬物動態である。本発明に係る投与形態が、生物学的等価性の限界内で約１００％の絶対生物学的利用能を有することが測定された。したがって、例えば、パロノセトロンの０．７５ｍｇ注射が約５８２８５（ｎｇ・時間／Ｌ）の平均ＡＵＣ（０→∞）を作り出し、一方、０．７５ｍｇのゲルキャップは約５７４０３（ｎｇ・時間／Ｌ）の平均ＡＵＣ（０→∞）を作り出す。これに反し、０．７５ｍｇゲルキャップの平均C_{max}は約１２２４ｎｇ／Ｌであり、一方、０．７５ｍｇ注射は約１６６５ｎｇ／Ｌの平均C_{max}を作り出す。０．５ｍｇゲルキャップは、約３８１７６（ｎｇ・時間／Ｌ）の平均ＡＵＣ（０→∞）、及び約８１０ｎｇ／Ｌの平均C_{max}を作り出すことが示され、それにより、投与量に比例する薬物動態が説明される。

【0045】

それゆえ、さまざまな態様において、本発明に係る投与形態は、再び生物学的等価性の制限内で算術平均として、９０，９５、又はさらに９８％超の絶対生物学的利用能を作り出す。あるいは又はさらに、５０ｍｇゲルキャップは、約７００～約９５０ｎｇ／ｍｌの、又は約７５０～約８７５ｎｇ／ｍｌの平均C_{max}を作り出す。最も好ましい態様においては、５０ｍｇゲルキャップは、好ましくは生物学的等価性の制限内で８００～８２０ｎｇ／Ｌの、C_{max}を作り出す。本発明に係る投与形態は投与量に比例する薬物動態を示すので、これらのC_{max}値は、投与形態の強さに基づき標準化されることができ、そしてC_{max}値は、このような標準化に基づき他の強さに割り当てられることができると理解されよう。

【0046】

本発明の態様の内のいずれかにおいても好ましい、本発明に係る投与形態のさらに他の重要な特徴は、投与形態の溶解に関係し、そして好ましい態様においては、５００ｍｌの０．０１Ｎ　ＨＣｌ中７５ｒｐｍ３７℃で米国薬局方に従うタイプIIパドル溶解装置内で試験されるとき、投与形態中のパロノセトロンの約７５％以上が３０又は４５分で溶解する。

【0047】

本発明の態様の内のいずれかにおいても好ましい、本発明に係る投与形態のさらに他の特徴は、投与形態又は充填タイプ又は製造方法に拘らず、湿度耐性パッケージング内の投与形態が、３ヶ月、６ヵ月、９ヶ月又はさらに１年に等しい又はそれよりも長い期間、２５℃６０％ＲＨ、又は４０℃７５％ＲＨの環境に晒されるとき、投与形態が、パロノセトロンの５ｗｔ％，３ｗｔ％、又は２ｗｔ％以下の分解を経験するということである。

【0048】

塩酸パロノセトロン及び関連化合物

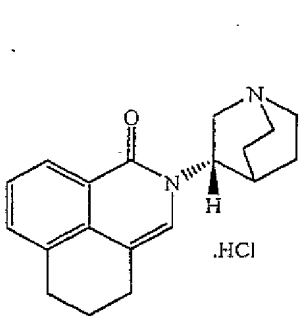
本発明において使用されるパロノセトロンは、塩基又は医薬として許容される塩としてのパロノセトロンであることができるが、好ましくは塩酸パロノセトロンである。さらに、パロノセトロンは、医薬として許容される塩として存在するとき塩基の重量に基づき、好ましくは、投与形態当り約０．０２ｍｇ～約１０ｍｇの、より好ましくは、投与形態当り約０．０５又は０．１５～約２ｍｇの、そしてさらにより好ましくは、投与形態当り約０．２～約１．０ｍｇの範囲の量で存在する。特に好ましい投与量は、塩基の重量に基づき、０．２５ｍｇ，０．５０，及び０．７５ｍｇのパロノセトロン又はその塩である。特

に安定した配合品は、約０．２５，０．３５又は０．４５ｍｇ超、好ましくは約２．０ｍｇ未満の、液体ゲルキャップ中のパロノセトロン量を用いる場合に見られた。

【0049】

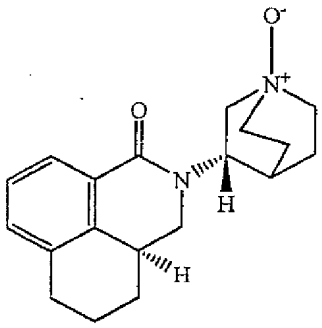
投与形態を作製するために使用され、又は最終投与形態中に含有される塩酸パロノセトロンは、以下の化学構造により示されるような化合物Ｃｐｄ３，Ｃｐｄ２、及び／又はＣｐｄ１を含む各種パロノセトロン関連化合物の存在によっても特徴付けられる：

【化2】



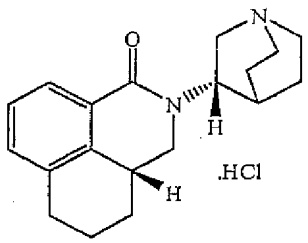
2-[(3S)-1-アザビシクロ[2.2.2]オクト-3-イル]-2,4,5,6-テトラヒドロ-1H-ベンゾ[de]イソキノリン-1-オン ヒドロクロリド

Cpd2



(3S)-3-[(3aS)-1-オキソ-2,3,3a,4,5,6-ヘキサヒドロ-1H-ベンゾ[de]イソキノリン-2-イル]-1-アゾニアビシクロ[2.2.2]オクタン-1-オレエート

Cpd1



(3aR)-2-[(S)-1-アザビシクロ[2.2.2]オクト-3-イル]-2,3,3a,4,5,6-ヘキサヒドロ-1-オキソ-1H ベンズ[de]イソキノリン ヒドロクロリド

Cpd3

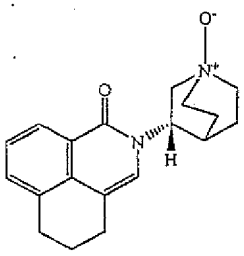
【0050】

化合物Ｃｐｄ２とＣｐｄ３は、典型的には、塩酸パロノセトロンに対して個々又は併合基準で、１．０ｗｔ％，０．７５ｗｔ％又は０．５ｗｔ％未満の、そして／又は約０．０５ｗｔ％，０．０７５ｗｔ％又は０．１ｗｔ％超の量で存在する。Ｃｐｄ２とＣｐｄ３は、投与形態中で、又は投与形態を作るために使用されるパロノセトロン原材料中で計測されうる。化合物Ｃｐｄ１は典型的には、塩酸パロノセトロンに対して個々の基準で、約０．０５ｗｔ％，０．１ｗｔ％又は０．２ｗｔ％超、そして／又は約３．０ｗｔ％，２．５ｗｔ％，１．５ｗｔ％，１．０ｗｔ％、又は０．５ｗｔ％未満の量で存在する。Ｃｐｄ１は、酸素仲介分解の尺度であるので、好ましくは、投与形態中で計測される。１の好ましい態様においては、投与形態は、化合物Ｃｐｄ１の約５．０ｗｔ％，４．０ｗｔ％，３．０ｗｔ％，２．５ｗｔ％，２．０ｗｔ％，１．５ｗｔ％，１．０ｗｔ％。、又は０．５ｗｔ％以下が、３ヶ月、６ヵ月、９ヶ月、又はさらに１年以上の期間にわたり、２５℃６０％ＲＨ又は４０℃７５％ＲＨの環境にその湿度抵抗性パッケージング内の投与形態が晒されるときに、形成されるところの安定性により定義される。

【0051】

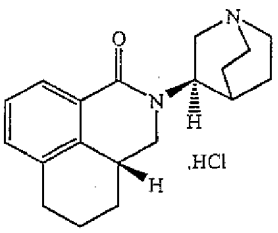
それゆえ、他の態様においては、本発明は、（ａ）約０．０５～約２．０ｍｇのパロノセトロン又は医薬として許容されるその塩；（ｂ）１以上の医薬として許容される賦形剤；（ｃ）パロノセトロンの重量に基づき３．０ｗｔ％未満の量のＣｐｄ１；を含む固体経口投与形態を提供する。他の態様においては、本発明は、（ａ）約０．０５～約２．０ｍｇのパロノセトロン又は医薬として許容されるその塩；（ｂ）１以上の医薬として許容される賦形剤；（ｃ）パロノセトロン又は医薬として許容されるその塩の重量に基づき、１．０ｗｔ％未満の量のＣｐｄ２又はＣｐｄ３を含む固体投与形態を提供する。これらの態様の内のいずれかにおいては、投与形態は、場合により、上記パロノセトロンの酸素仲介分解を防止するための手段を含みうる。

【0052】
上記組成物中に存在しうる他のパロノセトロンの関連化合物は、以下に示すＣｐｄ４，Ｃｐｄ５，Ｃｐｄ６、及びＣｐｄ７を含む：
【化3】



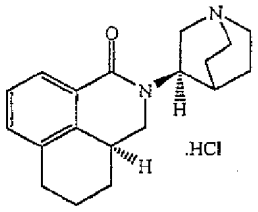
(3S)-3-(1-オキソ-2,4,5,6-テトラヒドロ-1H-ベンゾ[de]イソキノリン-2-イル)-1-アゾニアビシクロ[2.2.2]オクタン-1-オレエート

Cpd4



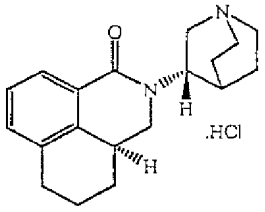
(3aR)-2-[(R)-1-アザビシクロ[2.2.2]オクト-3-イル]-2,3,3a,4,5,6-ヘキサヒドロ-1-オキソ-1H-ベンズ[de]イソキノリンヒドロクロリド

Cpd5



(3aS)-2-[(R)-1-アザビシクロ[2.2.2]オクト-3-イル]-2,3,3a,4,5,6-ヘキサヒドロ-1-オキソ-1H-ベンズ[de]イソキノリンヒドロクロリド

Cpd6



(3aS)-2-[(R)-1-アザビシクロ[2.2.2]オクト-3-イル]-2,3,3a,4,5,6-ヘキサヒドロ-1-オキソ-1H-ベンズ[de]イソキノリンヒドロクロリド

Cpd7

【0053】
製造方法
本発明は、パロノセトロン投与形態の製造方法をも提供する。したがって、さらに他の態様においては、本発明は、（ａ）塩酸パロノセトロン及び１以上の医薬として許容される賦形剤を混合して混合物を形成し；（ｂ）上記混合物を「処理」して複数の最終投与形態にし；そして（ｃ）Ｃｐｄ２，Ｃｐｄ１、及びＣｐｄ３から選ばれる１以上のパロノセトロン関連化合物について上記最終投与形態の内の１以上を試験する；を含む、不純物及び酸素仲介分解産物の量が低下されたパロノセトロン投与形態のバッチの製造方法を提供する。「処理」とは、所定の成分セットから医薬配合品及び最終投与形態を調製するために使用されるステップをいい、そして配合品中に使用される成分を化学的に合成するプロセスを除く。この態様は、例えば、滅菌された注射溶液を満たされたパロノセトロンの単一の単位投与形態アンプルを含む、パロノセトロンの全ての投与形態まで拡大される。したがって、例えば、本発明は、好ましくは水性媒質中のパロノセトロンの滅菌注射溶液、及び好ましくはCalderari et al.のＷＯ２００４／０６７００５中に記載されるように配合されたもので、単位投与アンプル又は容器を満たすための方法にも拡大されうる。この文脈中「アンプル」とは、１回だけ使用される投薬の小さな密封された容器を意味し、割れる又は割れないガラスアンプル、割れるプラスチックアンプル、ミニチュア・スクリューートップ・ジャー、及びパロノセトロンの１単位投与量のみ（典型的には約５ｍｌ）を保持することができるサイズのいずれかの他のタイプの容器を含む。
【0054】
他の態様は、生物学的利用能と安定性に関し、本発明に係る配合品により達成されるバランスを捕獲し、そしてこの態様においては、本発明は（ａ）約１．０×１０$^{-3}$ｍｌ・ｃｍ／（ｃｍ^2・２４時間・ａｔｍ）未満の酸素透過性を有するソフトゼラチン外部シェルを提供し；そして（ｂ）以下の：（ｉ）約０．０５～約２．０ｍｇの、塩酸パロノセトロンとしてのパロノセトロンを提供し、ここで上記パロノセトロンは、当該パロノセトロンの重量に基づき、１．０ｗｔ％未満の量のＣｐｄ１を含み；（ii）上記パロノセトロンを水に溶解し又は分散させて、水性プレミックスを形成し；（iii）上記水性プレミックスを１以上の親油性賦形剤と、水性プレミックス対親油性賦形剤５０：５０，４０：６０，

３０：７０、又は２０：８０未満の重量比で混合して、混和性又は均質親油性充填組成物を形成し；（iv）界面活性剤を上記水、上記水性プレミックス、又は上記充填組成物と混合し；そして（ｖ）上記充填組成物中の界面活性剤と水の量をバランスさせて、経口摂取されたときの上記ゼラチンカプセルからのパロノセトロンの生物学的利用能を促進し、そしてパロノセトロン分解の程度を最小化する；を含むステップにより充填組成物を調製し；そして上記充填組成物を上記外部シェルに充填する；を含む、パロノセトロンゼラチンカプセル内のパロノセトロンの生物学的利用能及び安定性を最適化する方法を提供する。

【0055】

本発明に係るさらに他の方法は、（ａ）空のシェルを提供し；そして（ｂ）上記シェル容器を、酸素消耗周囲環境下で、充填組成物で満たすことを含むパロノセトロン投与形態のパッケージング方法であって、上記充填組成物が（ｉ）パロノセトロン又は医薬として許容されるその塩を含む活性成分組成物の所定量と；（ii）医薬として許容される賦形剤とを含む前記方法を提供する。「酸素消耗環境」とは、好ましくは、（重量又は体積基準で）約１０％，５％又はさらに１％又は０．１％未満の酸素含有量により規定されるものである。さらにより好ましい態様においては、本発明に係る投与形態の製造又はパッケージング方法は、窒素ブランケット又はパージ下で（重量又は体積基準で）約９０％，９５％、又は９８％超の窒素を含む窒素に富んだ環境下で行われる。

【0056】

他の特別な態様においては、本法は、投与形態の中での活性成分の可変性により定められ、ここで、複数の固体投与形態の製造方法が提供され、該方法は、（ａ）カプセルシェルを提供し；（ｂ）上記カプセルシェルを、（ｉ）所定量のパロノセトロン又は医薬として許容されるその塩；及び（ii）医薬として許容される賦形剤を含む充填組成物で満たし；そしてステップ（ａ）と（ｂ）をさらに１回以上繰り返すステップを含み、ここで上記所定量は、約3，２，１，０．５又は０．１ｗｔ％未満のカプセル対カプセルのバラツキを有する。

【0057】

以上の態様のいずれかにおいて、製造方法は、湿度抵抗性の密封された容器内に上記投与形態又は複数の投与形態をパッケージングすることをさらに含むこともできる。湿度抵抗性密封容器を形成するために使用される材料は、好ましくは、約１．０×１０$^{-2}$，１．０×１０$^{-3}$，１．０×１０$^{-4}$、又はさらに５．０×１０$^{-5}$ｍｌ・ｃｍ／（ｃｍ^{2}・２４時間・ａｔｍ）未満の酸素透過性を有する。あるいは又はさらに、パッケージングは、ＵＳＰ＜６７１＞中に記載された標準下の「気密容器」として特徴付けられうる（すなわち、１０個の試験された容器の内１以下が、水分透過性において１００ｍｇ／日／Ｌを超え、そして全てが２００ｍｇ／日／ｍｌを超えない）。さらに、容器は、本発明に係る投与形態が保存の間に吸収することを可能にする水分量により規定されうる。例えば、さまざまな好ましい態様において、容器は、投与形態が、４０℃７５％相対湿度で保存されるとき、３ヶ月間で１．０，０．１又はさらに０．０５ｗｔ％を超える水分を吸収することを妨害する。ブリスターパッケージングが、特に好ましいパッケージングのモードである。

【0058】

ソフトゼラチンカプセル

本発明の液体コア医薬組成物は、以下に記載するソフトゼラチンシェル内にカプセル化される。ゼラチンは、本発明のソフトゼラチンシェルの好ましい成分である。出発ゼラチン材料は、コラーゲン様物質、例えば、動物の皮膚、白色結合組織、又は骨の部分的加水分解により得られうる。ゼラチン材料は、タイプＡのゼラチンとして分類されることができ、これは、ブタの皮膚の酸処理から得られ、そしてｐＨ７とｐＨ９の間の等電点を示し；そしてタイプＢのゼラチンとして十分類され、これは骨又は動物（ウシ）皮膚のアルカリ処理から得られ、そしてｐＨ４．７とｐＨ５．２の間の等電点を示す。タイプＡゼラチンとタイプＢゼラチンのブレンドも、カプセル製造のための必要な粘度及びブルーム（bloom）強度特性をもつゼラチンを得るために使用されうる。カプセル製造に好適なゼラチンは、the Sigma Chemical Company, St, Louis, Moから商業的に入手可能である。ゼラ

チン及びゼラチンベースのカプセルの一般的説明については、Remington's Pharmaceutical Sciences, 16th ed. , Mack Publishing Company, Easton, Pa. （1980）, pages 1245 and pages 1576-1582；及び１９９０年６月１９日にBorkan et al. に発行された米国特許第４，９３５，２４３号を参照のこと；これらの２つの文献を全体として本明細書中に援用する。

【0059】

ソフトゼラチンシェルは、約２０％～約６０％のゼラチンを含みうる。ゼラチンはタイプＡ又はタイプＢであるか、又はその混合物であることができ、約６０～約３００の範囲のブルーム数（bloom numbers）をもつ。ソフトゼラチンシェルは、可塑剤を含んでもよい。有用な可塑剤は、グリセリン、ソルビタン、ソルビトール、又は同様な低分子量ポリオール、及びそれらの混合物を含む。本発明において有用な好ましい可塑剤はグリセリンである。本発明のソフトゼラチンシェルは、水を含んでもよい。いずれかの理論にも拘束されないが、水は、体内で胃腸液と接触するとき、ソフトゼラチンシェルの速い溶解又は破壊を助けると信じられる。

【0060】

ソフトゼラチンカプセル及びカプセル化方法は、P. K. Wilkinson et at. , “Softgels：Manufacturing Considerations”, Drugs and the Pharmaceutical Sciences, 41（Specialized Drug Delivery Systems）, P. Tyle, Ed. （Marcel Dekker, Inc. , New York, 1990）pp. 409-449；F. S. Horn et at. , “Capsules, Soft”, Encyclopedia of Pharmaceutical Technology, vol. 2, J. Swarbrick and J. C. Boylan, eds. （Marcel Dekker, Inc. , New York, 1990）pp. 269-284；M. S. Patel et 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）；及び W. R. Ebert, “Soft Elastic Gelatin Capsules：A Unique Dosage Form” Pharmaceutical Technology, vol. 1, no. 5, pp. 44-50（1977）中に記載されており；これらの文献を全体として本明細書中に援用する。得られるソフトゼラチンカプセルは、水及び胃腸液中で可溶性である。カプセルを飲み込むと、ゼラチンシェルは、胃腸管内で速やかに溶解又は破壊し、それにより液体コアから体内へ医薬活性剤が導入される。

【0061】

治療方法

さらなる態様において、本発明は、本明細書中に記載する投与形態の内の１以上を投与することにより吐き気を治療する方法を提供する。吐き気は、急性期の吐き気（すなわち、吐き気誘導事件から約２４時間以内に経験する吐き気）、又は遅れた吐き気（すなわち、急性期の後であるが、吐き気誘導事件から７，６，５又は４日以内に経験する吐き気）であることができる。吐き気は、中程度又は高程度の吐き気を引き起こす化学療法からの、化学療法誘導吐き気及び嘔吐（ＣＩＮＶ）、放射線治療誘導吐き気及び嘔吐（ＲＩＮＶ）、又は術後吐き気及び嘔吐（ＰＯＮＶ）を構成しうる。

【0062】

生物学的等価性試験

製品が、「生物学的等価性の制限内で」特別な薬物動態パラメーターを示すと言われるとき、当該製品は、本明細書中で特定する生物学的等価性試験を用いる試験薬物に生物学的に等価である。生物学的等価性試験は、典型的には、全血、血漿、血清、又は他の適当な生物学的液体中の、活性成分（active ingredient or active moiety）、及び適当な場合、その活性代謝産物の濃度が時間の関数として計測されるところのヒトにおけるインビボ試験を要求する。相対的生物学的利用能（ＢＡ）として定義される生物学的等価性（ＢＥ）は、試験と参照医薬製品の間の比較を含む。ＢＡとＢＥは密着に関係するけれども、ＢＥは、通常、（１）基準、（２）当該基順についての信頼区間、及び（３）予め測定さ

れたＢＥ制限に、頼る。
【0063】
標準的なインビボＢＥ試験デザインは、医薬製品の投与の２つの可能性のある順番に無作為に割り当てられた、別個の機械における健康対象者に対する試験製品と参照製品の単一又は多数の投薬のいずれかの投与に基づく。薬物動態計測値、例えば、曲線下面積（ＡＵＣ）とピーク濃度（C_{max}）の統計学的分析は、好ましくは、試験製品及び参照製品の投与後に測定された薬物動態計測値の平均値が比較しうるものであるか否かを決定するためのいわゆる「２つの片側検定手順」に基づく。このアプローチは、平均生物学的等価性といわれ、そして試験製品と参照製品についての計測値の平均（集団幾向平均）の比について９０％信頼区間を計算することを含む。ＢＥを確立するためには、計算された信頼区間は、ＢＥ制限内、すなわち、製品平均の比について８０～１２５％内になければならない。したがって、例えば、生物学的等価性は、所定の環境セット下、８０～１２５％の間のＡＵＣについての９０％信頼区間、及び８０～１２５％の間のC_{max}についての９０％信頼区間により、確立されると言われる。
【0064】
ＢＥ手順に関するさらなる詳細は、“Statistical Procedures for Biolquiralence Studies Using a Standard Two-treatment Crossover Design”と題するＦＤＡの１９９２年７月のガイダンス文書中に見られ；その内容を本明細書中に援用する。
【実施例】
【0065】
実施例
以下の実施例は、当業者に、本願請求に係る化合物をどのように製造し、そして評価するかについての完全な開示及び説明を提供し、そして本発明の純粋な例示であると意図され、そして本願発明者らが本発明として考えるものの範囲を限定することを意図されない。数（例えば、量、温度等）に関して正確さを保証する努力を試みたが、いくらかの誤差及び偏差が原因とされるであろう。別段の記載なき限り、部は重量部であり、温度は℃又は室温におけるものであり、そして圧力は大気圧下及びそれ付近である。
【0066】
実施例１－代表的ゲル－キャップ配合品
表１は、０．２５，０．５０、及び０．７５ｍｇのパロノセトロンを含有するゲル－キャップ固体経口投与形態の代表的な配合品を説明する。
【0067】

【表1】

表１．代表的ゲルーキャップ配合品

成分名	処方(カプセル当りmg)		
	0.25mg	0.50mg	0.75mg
活性医薬物質 パロノセトロン	0.28[a]	0.56[b]	0.84[c]
賦形剤 精製水	5.57	5.57	5.57
グリセリン、無水	6.40	6.40	6.40
ブチル化ヒドロキシアニソール(BHA)	0.13	0.13	0.13
オレイン酸ポリグリセリル (Plurol Oleique CC 497)	6.65* (1.66)**	6.65* (1.66)**	6.65* (1.66)**
カプリル/カプリン酸のモノ－及び ジ－グリセリド (Capmul MCM)	113.97* (118.96)**	113.69* (118.68)**	113.41* (118.40)**
窒素	---	---	---
理論充填量	133.00mg	133.00mg	133.00mg
ゼラチンカプセルシェル、#3、オーバル (Cardinal Health)	1カプセル	1カプセル	1カプセル

[a] 0.25mg遊離塩基に相当する
[b] 0.50mg遊離塩基に相当する
[c] 0.75mg遊離塩基に相当する
* 配合品A(臨床バッチ)
** 配合品B(商業バッチ)

【0068】
実施例２－製造プロトコール
配合プロセスは、２つの別々の混合物の配合、すなわち、活性成分、グリセリン、及び水を含有する副ミックス、並びに残余の賦形剤を含有する主ミックスの配合を含む。プロセスは上記２つの別々のミックスから出発し、そしてこれらはその後に混合されて、カプセル化のための最終充填溶液が作られる。この充填溶液は、配合及びカプセル化期の間、窒素下で覆われる。
【0069】
実施例３－代表的溶解試験プロトコール
パロノセトロン経口カプセル０．２５ｍｇ，０．５０ｍｇ、及び０．７５ｍｇの例示的溶解法法は、３７．０±０．５℃の溶解温度で５００ｍＬの０．０１Ｎ　ＨＣｌ中７５ｒｐｍでＵＳＰ装置２（パドル）を使用する。許容基準は、「４５分で７５％以上」である。
６つのソフトゲルーカプセルを個々に計重する。ソフトゲルカプセルを各容器内に入れ、そして１５，３０，４５、及び６０分でサンプル採取する。１５，３０，６０分におけ

るサンプリングは、情報のみのためである。サンプル溶液を取り出し、そして試験管内又はＨＰＬＣバイアル内にオンラインフィルターを通して沪過する。サンプルを、ＵＶ検出器を備えたＨＰＬＣシステムを使用して分析する。

【0070】

【表2】

表２．溶解条件

USP装置	2パドル
媒質	0.01N HCl，500mL
温度	37±0.5℃
回転速度	75rpm
サンプリング時間	45分 15，30、及び60分(情報のみのため)
サンプリング体積	3mL(又は1-1.5mL HPLC バイアル内に直接採取するとき)
体積	500mL 溶解媒質

【0071】

実施例４－化学及び物理学的安定性

表３は、２×５ブリスター・ユニット（Forming：ＬＭ１５０８８，Foil：Reynolds 701）内に包装された、実施例１において報告された０．７５ｍｇパロノセトロンソフトゲル配合品を化学及び物理学的安定性試験の結果を示す。

【0072】

【表3】

表３．化学的及び物理的安定性

試験	パロノセトロン・アッセイ		パロノセトロン関連物質			溶解試験（%溶解）			
仮仕様	90.0-110.0%	% vs t0	Cpd3	Cpd2	Cpd1	45分	15分	30分	60分
			≦0.50%	≦0.50%	≦3.0%	NLT 75%	情報のみのため	情報のみのため	情報のみのため
開始値	97.7	100.0	0.28	0.28	0.20	98.5	70.4	97.7	98.9
25℃/60% r.h.									
03ヶ月	97.6	99.9	0.23	0.26	0.23	99.2	97.6	99.1	98.8
06ヶ月	96.5	98.8	0.26	0.27	0.46	97.6	87.4	97.2	97.7
09ヶ月	96.0	98.3	0.23	0.27	0.6	99.0	80.5	98.9	99.1
12ヶ月	93.7	95.9	0.22	0.26	0.6	96.8	81.9	96.5	96.7
40℃/75% r.h.									
01ヶ月	97.2	99.5	0.36	0.25	0.56	99.9	92.3	100.5	100.1
03ヶ月	97.5	99.8	0.24	0.26	0.65	97.3	79.9	97.0	97.5
06ヶ月	96.2	98.5	0.26	0.27	0.68	96.9	52.5	96.7	97.0

【0073】

実施例５－化学及び物理学的安定性

表４は、２×５ブリスター・ユニット（Forming：ＬＭ１５０８８，Foil：Reynolds 701）内に包装された、実施例１において報告された０．５０ｍｇパロノセトロンソフトゲル配合品の化学及び物理学的安定性試験の結果を示す。

【0074】

【表4】

表４．化学的及び物理的安定性

試験	パロノセトロン・アッセイ		パロノセトロン関連物質			溶解試験(%溶解)			
仮仕様	90.0-110.0%	% vs t0	Cpd3	Cpd2	Cpd1	45分	15分	30分	60分
			≦0.50%	≦0.50%	≦3.0%	NLT 75%	情報のみのため	情報のみのため	情報のみのため
開始値	97.9	100.0	0.28	0.26	0.16	98.9	69.1	99.9	99.2
25℃/60% r.h.									
03ヶ月	97.5	99.6	0.23	0.26	0.44	100.1	86.0	100.0	100.1
06ヶ月	97.2	99.3	0.27	0.28	0.37	97.6	41.4	88.3	97.6
09ヶ月	96.5	98.6	0.22	0.28	0.5	99.0	83.0	97.8	99.1
12ヶ月	94.7	96.7	0.22	0.27	0.5	96.9	85.6	96.7	97.0
40℃/75% r.h.									
01ヶ月	97.3	99.4	0.29	0.27	0.42	102.6	65.8	101.1	102.8
03ヶ月	97.3	99.4	0.24	0.26	0.55	100.0	39.8	94.2	99.0
06ヶ月	96.6	98.7	0.26	0.27	0.67	97.0	52.7	96.7	97.2

【0075】

実施例６－化学及び物理学的安定性

表5は、２×５ブリスターユニット（Forming：ＬＭ１５０８８，Foil：Reynolds 701）内に包装された、実施例１において報告された０．２５ｍｇパロノセトロンソフトゲル配合品の化学及び物理学的安定性試験の結果を示す。

【0076】

【表5】

表５．化学的及び物理的安定性

試験	パロノセトロン・アッセイ		パロノセトロン関連物質			溶解試験(%溶解)			
仮仕様	90.0-110.0%	% vs t0	Cpd3	Cpd2	Cpd1	45分	15分	30分	60分
			≦0.50%	≦0.50%	≦3.0%	NLT 75%	情報のみのため	情報のみのため	情報のみのため
開始値	97.7	100.0	0.29	0.29	0.38	97.2	61.8	97.4	97.7
25℃/60% r.h.									
03ヶ月	97.4	99.7	0.24	0.26	0.92	98.6	98.0	99.1	99.1
06ヶ月	95.9	98.2	0.28	0.27	1.10	95.2	82.3	94.8	95.7
09ヶ月	94.7	96.9	0.21	0.28	1.4	94.5	89.2	93.9	94.6
12ヶ月	94.5	96.7	0.23	0.27	1.7	96.2	97.1	96.1	96.1
40℃/75% r.h.									
01ヶ月	96.3	98.6	0.29	0.27	1.42	99.4	88.2	99.5	97.7
03ヶ月	97.4	99.7	0.24	0.25	1.85	97.4	78.7	97.6	97.5
06ヶ月	94.0	96.2	0.27	0.26	1.94	96.8	82.6	96.2	97.0

【0077】

実施例７－代表的注射用配合品

以下の表６は、パロノセトロンを含有する代表的な注射用配合品を説明する。

【0078】

【表6】

表６．代表的な注射用配合品

成分	mg/mL
塩酸パロノセトロン	0.05(塩基として計算)
マンニトール	41.5
EDTA	0.5
クエン酸3ナトリウム	3.7
クエン酸	1.56
WFJ	1.0
水酸化ナトリウム溶液、及び/又は塩酸溶液	pH5.0±0.5
香料	q.s.

【0079】

実施例８－ＵＶ検出品を備えたＨＰＬＣによるパロノセトロンＨＣｌソフトゲル内のパロノセトロンの同定及びアッセイ

試験手順

ＨＣｌ０．０１Ｎ中６．２５μｇ／ｍｌのパロノセトロンＨＣｌ各目濃度においてサンプル及び標準溶液を調製する。

溶液を沪過し、そしてＨＰＬＣシステム内にインジェクトする。

ＨＰＬＣ条件

カラム	Ｃ８，２５０ｍｍ×４．６（ｉ．ｄ．）
カラム温度	３０℃
移動相	ＡＣＮ／H_2O／ＴＦＡ、グラジエント溶出
フローレート	１ｍＬ／分
検出	２１０ｎｍにおけるＵＶ
インジェクション体積	２０μＬ

【0080】

実施例９－パロノセトロンＨＣｌソフトゲル内のパロノセトロン関連化合物の測定、及びソフトゲル充填溶液のイン－プロセス・アッセイ

試験手順

メタノール中０．１５ｍｇ／ｍＬのパロノセトロンＨＣｌ各目濃度でサンプル及び標準溶液を調製する。

溶液をＨＰＬＣシステム内に直接インジェクトする。

ＨＰＬＣ条件

カラム	Ｃ８，２５０ｍｍ×４．６（ｉ．ｄ．）
カラム温度	３０℃
移動相	ＡＣＮ／H_2O／ＴＦＡ、グラジエント溶出
フローレート	１ｍＬ／分
検出	２１０ｎｍにおけるＵＶ
インジェクション体積	１０μＬ

【0081】

実施例１０－ＵＶ検出器を備えたキラルＨＰＬＣによるパロノセトロンＨＣｌソフトゲル内のパロノセトロン関連化合物の測定

試験手順

メタノール中０．３４ｍｇ／ｍＬのパロノセトロンＨＣｌ各目濃度でサンプル溶液を調

製する。
５．６μｇ／ｍＬの各目濃度でＣｐ２標準溶液を調製する。
メタノール溶媒中、８μｇ／ｍＬの各目濃度で、Resolution溶液を調製する：Ｃｐｄ２，Ｃｐｄ４，Ｃｐｄ５，Ｃｐｄ６、及びＣｐｄ７の濃度は約０．４μｇ／ｍＬである。
溶液をＨＰＬＣシステム内に直接インジェクトする。

ＨＰＬＣ条件

カラム	キラルカラム
カラム温度	３５℃
移動相	ＡＣＮ／ＭｅＯＨ／ＩＰＡ／ＡｃＯＨ／ＴＥＡ、アイソクラティック溶出
フローレート	１ｍＬ／分
検出	２３８ｎｍにおけるＵＶ
インジェクション体積	１０μＬ

【0082】
実施例１１－ＨＰＬＣによるパロノセトロンＨＣｌソフトゲルの溶解
試験手順
ＨＣ１０．０１Ｎ中１μｇ／ｍＬのパロノセトロンＨＣｌ各目濃度で標準溶液を調製する。
サンプル溶液：５００ｍＬの０．０１Ｎ　ＨＣｌを含有する容器内に１つのソフトゲルカプセルを入れる。
溶液を沪過し、そしてＨＰＬＣシステム内にインジェクトする。

ＨＰＬＣ条件

カラム	Ｃ８，１５０ｍｍ×４．６ｍｍ（ｉ．ｄ．）
カラム温度	３０℃
移動相	ＡＣＮ／H_2O／ＴＦＡ、グラジエント溶出
フローレート	１ｍＬ／分
検出	２１０ｎｍにおけるＵＶ
インジェクション体積	５０μＬ

【0083】
実施例１２－０．７５ｍｇのゲルキャップ及び注射用投与形態の生物学的等価性
生物学的等価性と絶対生物学的利用能を、健康なボランティアにおける０．７５ｍｇパロノセトロンの２つの配合品の単一経口投与において試験した。試験は、３つの処理、３つの期間、２つの順番交差試験であった。
処理Ａは、表１に示す臨床ゲルキャップ配合品における０．７５ｍｇのパロノセトロンの単一投与を表した。
処理Ｂは、表１中の商業的ゲルキャップ配合品における０．７５ｍｇのパロノセトロンの単一投与を表した。
処理ＩＶは、Ａｌｏｘｉ　２５ｍｇの３回連続ボーラス注射から構成された。
薬物動態パラメータを以下の表７中に報告する。
【0084】

【表7】

表７

薬物動態パラメーター パロノセトロン [unit]		0.75mg 経口投与 (配合品A) N＝33	0.75mg 経口投与 (配合品B) N＝33	0.75mg パロノセトロン 静脈内投与 (3×0.25mg i.v. Aloxi®) N＝30
$AUC_{(0-t)}$ [ng·h/L]	平均 (SD)	53835 (17961)	55235 (17817)	53088 (15233)
	幾同平均 (Geo. SD)	50716 (1.44)	52536 (1.39)	50793 (1.37)
	メジアン	50978	53325	50984
	最小-最大	16971-96273	20951-111916	20609-78424
$AUC_{(0-\infty)}$ [ng·h/L]	平均 (SD)	57403 (17898)	58285 (18110)	56480 (15343)
	幾同平均 (Geo. SD)	54539 (1.40)	55638 (1.37)	54324 (1.34)
	メジアン	54614	56802	54011
	最小-最大	18773-100234	24473-114765	24142-81547
C_{max} [ng/L]	平均 (SD)	1223.985 (348.324)	1200.620 (324.606)	1665.314 (527.638)
	幾同平均 (Geo. SD)	1178.670 (1.32)	1160.078 (1.31)	1588.758 (1.37)
	メジアン	1208.136	1133.115	1628.480
	最小-最大	570.494-2365.980	571.922-2130.740	890.742-2789.077
t_{max} [h]	メジアン	4.520	4.530	0.250
	最小-最大	2.000-8.000	2.000-12.030	0.250-4.030

【0085】
薬物動態を図１においても報告する。図中、b_1は、配合品Ａによる処理を表し、b_2は配合品Ｂによる処理を表し、そしてb_3はＡｌｏｘｉ　ｉ．ｖ．による処理を表す。図は、線状目盛り（ｎ＝３３）におけるパロノセトロンの算術平均血漿濃度（ｎｇ／ｍｌ）対時間（Ｈ）を報告する。

【0086】
実施例１３－５０ｍｇの臨床及び商業的ゲルキャップ配合品の生物学的等価性

生物学的等価性試験を、健康な男性及び女性ボランティアにおける０．５０ｍｇパロノセトロンのソフトゲルカプセル２つの配合品（配合品Ａと配合品Ｂ）の単一経口投与を評価するために企てた。この試験は、２つの処理、２つの期間、２つの順番、オープンラベル、無作為交差試験であった。

薬物動態を表８に報告する。

【0087】

【表8】

表８

薬物動態パラメーター パロノセトロン [unit]		0.50mg パロノセトロン 経口投与 (配合品A) N＝36	0.50mg パロノセトロン 経口投与 (配合品B) N＝36
AUC_{0-t} [ng·h/L]	平均 (SD)	34076 (9874)	35106 (11012)
	幾向平均 (Geo. SD)	32766 (1.33)	33530 (1.36)
	メジアン	33641	34981
	最小-最大	20085-60189	19003-72136
$AUC_{0-\infty}$ [ng·h/L]	平均 (SD)	37099 (10141)	38176 (11698)
	幾向平均 (Geo. SD)	35834 (1.30)	36555 (1.35)
	メジアン	36859	37627
	最小-最大	22439-62727	21240-77636
C_{max} [ng/L]	平均 (SD)	785.241 (182.437)	810.176 (165.985)
	幾向平均 (Geo. SD)	765.702 (1.25)	793.900 (1.23)
	メジアン	750.344	816.457
	最小-最大	463.862-1322.774	537.047-1258.878
t_{max} [h]	メジアン	5.500	5.000
	最小-最大	2.000-8.000	2.000-8.000

【0088】

薬物動態パラメータを図２にも報告する。図中、b_1は臨床配合品Ａを表し、そしてb_2は商業的配合品Ｂを表す。図は、線状目盛り（ｎ＝３３）におけるパロノセトロンの算術平均血漿濃度（ｎｇ／ｍｌ）対時間（Ｈ）を報告する。

【0089】

本願明細書の全体にわたり、さまざまな刊行物を引用した。これらの刊行物の開示を全体として本願明細書中に援用して、本願発明の属する技術の水準をより十分に説明する。本発明の本質又は範囲から逸脱せずにさまざまな変更又は修正が本願発明内でなしうることは当業者にとって明らかであろう。本発明の他の態様は、本願明細書を考慮し及び本願明細書中に開示された発明を実施することから当業者にとって明らかであろう。本願明細書及び実施例は例示としてのみ考慮され、そして本発明の範囲及び本質は添付のクレームにより画されると意図される。

【図面の簡単な説明】

【0090】

【図1】図１は、生物学的等価性試験からのヒト対象者において観察された薬物動態をプロットし、ここで、b_1は臨床配合品Ａによる処理を表し、b_2は商業的配合品Ｂによる処理を表し、そしてb_3はＡｌｏｘｉ（登録商標）ｉ．ｖ．による処理を表す。

【図2】図２は、生物学的等価性試験からのヒト対象者において観察される薬物動態をプロットし、ここで、b_1は臨床配合品Ａを表し、そしてb_2は商業的配合品Ｂ表す。図１と図２の両者は、線状目盛り（ｎ＝３３）におけるパロノセトロンの算術平均血漿濃度（ｎｇ／ｍｌ）対時間（Ｈ）を報告する。

【図1】

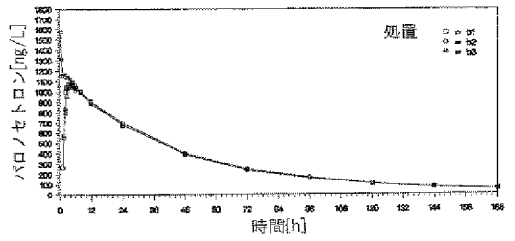


FIGURE 1

【図2】

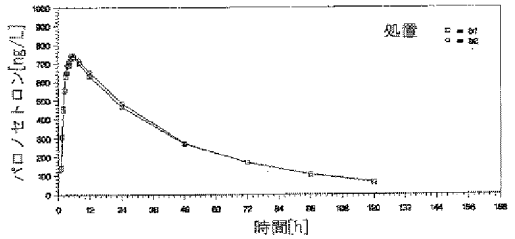


FIGURE 2

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)

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

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

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

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

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	GIMENEZ MIRALLES, J

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

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2007/009098

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004045615 A	03-06-2004	AU 2003302072 A1	15-06-2004
		CA 2505990 A1	03-06-2004
		DE 10393729 T5	13-10-2005
		JP 2006508977 T	16-03-2006
WO 2005065652 A	21-07-2005	CA 2547712 A1	21-07-2005
		EP 1706100 A1	04-10-2006
		JP 2007517859 T	05-07-2007
		US 2007190080 A1	16-08-2007
WO 02053131 A	11-07-2002	CA 2432362 A1	11-07-2002
		EP 1345590 A1	24-09-2003
		FR 2818905 A1	05-07-2002
		US 2004052824 A1	18-03-2004

Form PCT/ISA/210 (patent family annex) (April 2005)

(51)Int.Cl.			F I		テーマコード（参考）
Ａ６１Ｋ	47/36	(2006.01)	Ａ６１Ｋ	47/36	
Ａ６１Ｐ	1/08	(2006.01)	Ａ６１Ｐ	1/08	
Ａ６１Ｋ	47/14	(2006.01)	Ａ６１Ｋ	47/14	

(81)指定国　AP(BW,GH,GM,KE,LS,MW,MZ,NA,SD,SL,SZ,TZ,UG,ZM,ZW),EA(AM,AZ,BY,KG,KZ,MD,RU,TJ,TM),EP(AT,BE,BG,CH,CY,CZ,DE,DK,EE,ES,FI,FR,GB,GR,HU,IE,IS,IT,LT,LU,LV,MC,MT,NL,PL,PT,RO,SE,SI,SK,TR),OA(BF,BJ,CF,CG,CI,CM,GA,GN,GQ,GW,ML,MR,NE,SN,TD,TG),AE,AG,AL,AM,AT,AU,AZ,BA,BB,BG,BH,BR,BW,BY,BZ,CA,CH,CN,CO,CR,CU,CZ,DE,DK,DM,DO,DZ,EC,EE,EG,ES,FI,GB,GD,GE,GH,GM,GT,HN,HR,HU,ID,IL,IN,IS,JP,KE,KG,KM,KN,KP,KR,KZ,LA,LC,LK,LR,LS,LT,LU,LY,MA,MD,ME,MG,MK,MN,MW,MX,MY,MZ,NA,NG,NI,NO,NZ,OM,PG,PH,PL,PT,RO,RS,RU,SC,SD,SE,SG,SK,SL,SM,SV,SY,TJ,TM,TN,TR,TT,TZ,UA,UG,US,UZ,VC,VN,ZA,ZM,ZW

(74)代理人　100108903
弁理士　中村　和広
(74)代理人　100117019
弁理士　渡辺　陽一
(74)代理人　100150810
弁理士　武居　良太郎
(72)発明者　ボナデオ，ダニエレ
イタリア国，２１０３０　カサルツィニョ，バレーゼ，ビア　ロンコ　カポ　カッチア，３２
(72)発明者　カルデラリ，ジョルジオ
スイス国，６８６２　ランカテ，ビア　スチェル
(72)発明者　ブラリア，エンリコ
スイス国，６９１２　ルガーノ－パッツァロ，ビア　ピアン　スカイロロ　９
(72)発明者　ブラリア，リッカルド
スイス国，６９１２　ルガーノ－パッツァロ，ビア　ピアン　スカイロロ　９

Ｆターム(参考)　4C076 AA56 BB01 CC16 DD08F DD37 DD38E DD39E DD46F EE31H EE38H EE42H FF01 FF02 FF21 FF27 FF63 FF68 FF70 GG01 GG16
4C086 AA01 AA02 CB17 MA03 MA05 MA37 MA52 NA03 NA10 NA14 NA20 ZA71

Electronic Acknowledgement Receipt

EFS ID:	21215997
Application Number:	14069927
International Application Number:	
Confirmation Number:	3207
Title of Invention:	COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING
First Named Inventor/Applicant Name:	Fabio TRENTO
Customer Number:	6980
Filer:	Clark G. Sullivan/Dwight Peck
Filer Authorized By:	Clark G. Sullivan
Attorney Docket Number:	244168.000015US4
Receipt Date:	15-JAN-2015
Filing Date:	01-NOV-2013
Time Stamp:	11:19:02
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	PTO-IDSTransmittal-US4.PDF	84921 27121b5ced3d93fa667b1c5517246766ac13a039	no	4

Warnings:	
Information:	

2	Information Disclosure Statement (IDS) Form (SB08)	PTO-SB08-US4.PDF	1433114 eb13acc908891e228e2891829282d6f814225366	no	4
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
3	Foreign Reference	PTO-ART-JP2009507933A.PDF	1090417 658de9aaf3952519b82d7e6ba4b522d12a935e6a	no	30
Warnings:					
Information:					
4	Non Patent Literature	PTO-JPOAandEnglishtranslation.PDF	237068 a743d99298dcce66bba3f491304a2ae78f321501	no	4
Warnings:					
Information:					
5	Non Patent Literature	PTO-NPL-Hoffman.PDF	359712 3da06521c820a53c2c285a95b225958fc5b15096	no	4
Warnings:					
Information:					
		Total Files Size (in bytes):	3205232		

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.

Docket No.: 244168.000015US4
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Fabio TRENTO	Customer No.: 06980
Application No.: 14/069,927	Confirmation No.: 3207
Filing Date: November 1, 2013	Art Unit: 1612
For: COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING	Examiner: Walter E. WEBB

INFORMATION DISCLOSURE STATEMENT (IDS)

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

Dear Sir:

This Information Disclosure Statement is submitted in accordance with 37 C.F.R. 1.97, 1.98, and it is requested that the information set forth in this statement and in the listed documents be considered during the pendency of the above-identified application, and any other application relying on the filing date of the above-identified application or cross-referencing it as a related application.

1. This IDS should be considered, in accordance with 37 C.F.R. 1.97, as it is filed: (Check one of the boxes A-D)

- ☐ A. within three months of the filing date of the above-identified national application or within three months of the entry into the national stage of the above identified national application
- ☐ B. before the mailing date of a first office action on the merits, or a first office action after filing a request for continued examination.
- ☒ **C. after (A) and (B) above, but before final rejection or allowance, and Applicant has made the necessary statement in box "i" below or paid the necessary fee in box "ii" below.**

(check one of the boxes "i" and "ii" below:)

[X] **i. Counsel states that, upon information and belief, each item of information listed herein was (check one of boxes (a) or (b))**

[X] **(a) 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 this IDS;** or

[ ] (b) not cited in a communication from a foreign patent office in a counterpart foreign application and, to the knowledge of undersigned after making reasonable inquiry, was not known to any individual designated in 1.56(c) more than three months prior to the filing of this IDS.

[ ] ii. Please charge Deposit Account 20-1507 for the fee set forth in 1. 17(p), presently believed to be $180 ($90 for Small Entity).

[ ] D. after (A), (B) and (C) above, but before payment of the issue fee: Applicant petitions under 37 C.F.R. 1.97(d) for the consideration of this IDS. Under 37 CFR 1.17(p), please charge Deposit Account 20-1507 the fee of $180.00 ($90.00 for Small Entity). Counsel certifies that, upon information and belief, each item of information listed herein was

(check one of the boxes "a" and "b" below:)

[ ] (a) 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 this IDS; or

[ ] (b) was not cited in a communication from a foreign patent office in a counterpart foreign application and, to the knowledge of undersigned after making reasonable inquiry, was not known to any individual designated in 1.56(c) more than three months prior to the filing of this IDS.

2. In accordance with 37 C.F.R. 1.98, this IDS includes a list (e.g., form PTO/SB/08) of all patents, publications, or other information submitted for consideration by the office, either incorporated into this IDS or as an attachment hereto. A copy of each document listed is attached, except as explained below.

(check boxes A, B and/or C and fill in blanks, if appropriate.)

[X] **A. Pursuant to the Notice issued by the United States Patent and Trademark Office dated July 11, 2003 waiving the requirements of 37 C.F.R. § 1.98(a)(2)(i), a copy/copies of the United States Patent on PTO/SB08 is/are not being submitted.**

[ ] B. Document(s) _____is (are) deemed substantially cumulative to document(s) _____ , and, in accordance with 1.98(c), only a copy of each of the latter documents is enclosed.

[ ] C. Certain documents were previously cited by or submitted to the Office in the following prior applications, which are relied upon under 35 U.S.C. 120:

<<INSERT SERIAL NO. & FILING DATE>>

Applicant identifies these documents by attaching hereto copies of the forms PTO-892, PTO-1449 and/or PTO/SB/08 from the files of the prior application(s) or a fresh PTO/SB/08 listing these documents, and request that they be considered and made of record in accordance with 1.98(d). Per 37 CFR 1.98(d), copies of these documents need not be filed in this application.

[X] **3. Foreign Patent Document Cite No. 1 is not in the English language. In accordance with 1.98(c), Applicant states:**

[X] An English translation of each document (or of the pertinent portions thereof), or a copy of each corresponding English-language patent or application, or **English-language abstract** (or claim) **is enclosed**.

[ ] The requirement for a concise explanation of the relevance of any foreign language document is satisfied by the attached search report; citation of the documents cited in the search report shall not be construed as an admission that they are or are considered to be, material to patentability of the subject matter claimed herein (See MPEP §609).

[ ] A concise explanation of the relevance of document(s) _____ is set forth as follows: [Insert concise explanation of relevance]

[ ] A concise explanation of the relevance of document(s) _____ can be found on page(s) _____ of the specification.

[ ] A concise explanation of document(s) _____ can be found on the attached sheet.

[X] **4. No explanation of relevance is necessary for documents in the English language (see reply to Comments 67 in the preamble to the final rules; 1135 OG 13 at 20).**

[X] **5. Other information being provided for the examiner's consideration follows:**

Japanese Office Action dated November 19, 2014, which issued during prosecution of Japanese Application No. 2012-539433, which corresponds to the present application.

6. In accordance with 37 C.F.R. 1.97(g) and (h), the filing of this IDS should not be construed as a representation that a search has been made or that information cited is, or is considered to be, material to patentability as defined in §1.56 (b), or that any cited document listed or attached is (or constitutes) prior art. Unless other-wise indicated, the date of publication indicated for an item is taken from the face of' the item and Applicant reserves the right to prove that the date of publication is in fact different.

Early and favorable consideration is earnestly solicited.

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

Dated: January 15, 2015

Respectfully submitted,

/Clark G. Sullivan/

Clark G. Sullivan
Registration No.: 36,942
Troutman Sanders LLP
The Chrysler Building
405 Lexington Avenue
New York, New York 10174
Direct Tel: (212) 704-6105
Fax: (212) 704-6288
Direct E-mail:
clark.sullivan@troutmansanders.com
Attorneys/Agents for Applicant

Docket No.: 244168.000015US4
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Fabio TRENTO et al.	Customer No.: 06980
Application No.: 14/069,927	Confirmation No.: 3207
Filing Date: November 1, 2013	Art Unit: 1629
For: COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING	Examiner: Webb, Walter E.

AMENDMENT

Commissioner for Patents
Alexandria, VA

Dear Madam:

In response to the non-final Office Action mailed in the above-referenced application on November 28, 2014, please enter the following amendments and consider the following remarks.

A REPLACEMENT CLAIM SET begins on page 4 of this paper.

A TERMINAL DISCLAIMER will be filed as soon as Applicant files the necessary power of attorney paperwork.

A request for three month extension of time is being filed concurrently herewith.

Extra claims fees are being paid herewith.

Status of Claims

After this amendment, claims 52-113 are pending. Claims 52-67 were previously presented and rejected based solely on obviousness type double patenting. Claims 52-67 are not amended in this application. Claims 68-113, which are all dependent claims, are added by this Amendment. The various elements of claims 68-113, and their support in the specification, is summarized below:

LIMITATION	SPEC SUPPORT
CINV defined as no emetic episodes and no use of rescue medication	Par. [0115]
Single administration of netupitant without further administration for 5 days	Example 5
Single administration of palonosetron without further administration for 5 days	Example 5
Concomitant administration of netupitant and palonosetron	Example 5
Administration of netupitant and palonosetron prior to chemotherapy	Example 5
Regimen effective against CINV for 5 days	Example 5
Oral administration of 200-400 mg netupitant as free base	Par. [0059]
Oral administration of 0.25-0.75 mg of palonosetron hydrochloride	Par. [0061]
Oral administration of 300 mg netupitant as free base less than 2 hours prior to chemotherapy	Pars. [0059 and 0060]
Oral administration of 0.50 mg of palonosetron hydrochloride less than 2 hours prior to chemotherapy	Pars. [0060 and 0061]
Moderately emetogenic chemotherapy	Par. [0016]
Combination dosage form	Pars. [0068-71]
Dexamethasone 12 mg dose administered less than 2 hours before chemotherapy	Par. [0061]
Highly emetogenic chemotherapy	Par. [0016]
Dexamethasone 8 mg administered on days 2, 3 and 4	Par. [0061]
Netupitant occupies at least 70% of NK1 receptors in striatum 96 hours after administration	Par. [0059]
Netupitant effective during acute and delayed phases	Par. [0014]
Netupitant effective to treat nausea during acute and delayed phases	Table 6
(3S)-3-[(3aS)-1-oxo-2,3,3a,4,5,6-hexahydro-1H-benzo[de]isoquinoline-2-yl]- -1-azoniabicyclo[2.2.2]octan-1-olate substantially absent	Par. [0028]
Chemotherapy includes cisplatin	Par. [0048]
Chemotherapy includes carboplatin, cisplatin, oxaliplatin, or doxorubicin	Par. [0048]

Chemotherapy includes cyclophosphamide	[Par. 0048]
Regimen effective to treat nausea during acute and delayed phases	[Par. 0014]
If moderately emetogenic chemotherapy, only one dose of dexamethasone is administered for 5 days	[Pars. 0024 and 0025]
If highly emetogenic chemotherapy, a first dose of dexamethasone is administered on Day 1, and a second dose on days 2, and 4	Par. [0025]
Netupitant and the first dose of dexamethasone are administered prior to chemotherapy	Par. [0060]
Blood levels of netupitant are induced by intravenous anti-emetic regimen	Par. [0063]
Netupitant blood levels effective to treat CINV during acute and delayed phase	Table 5
Palonosetron blood levels effective to treat CINV during acute phase	Table 5

REPLACEMENT CLAIM SET

Claims 1 – 51. (Cancelled)

52) (Previously Presented) A method of treating chemotherapy induced nausea and vomiting (CINV) comprising administering to a subject receiving chemotherapy a regimen of palonosetron, netupitant and dexamethasone.

53) (Previously Presented) A method of treating chemotherapy induced nausea and vomiting (CINV) in a subject receiving chemotherapy comprising administering to a subject receiving chemotherapy a regimen of netupitant and a sub-therapeutic dose of dexamethasone.

54) (Previously Presented) The method of claim 53, wherein the sub-therapeutic dose of dexamethasone comprises from about 50 to 70% of a minimum effective dose when administered alone against CINV.

55) (Previously Presented) A method of treating chemotherapy induced nausea and vomiting (CINV) comprising inducing in a subject receiving chemotherapy blood levels of palonosetron and netupitant effective to treat said CINV.

56) (Previously Presented) The method of claim 52, wherein the chemotherapy comprises moderately or highly emetogenic chemotherapy.

57) (Previously Presented) The method of claim 52, wherein said chemotherapy comprises carboplatin.

58) (Previously Presented) The method of claim 52, wherein the netupitant and palonosetron are administered no more than one hour prior to administration of the chemotherapy.

59) (Previously Presented) The method of claim 52, wherein when said chemotherapy is highly emetic chemotherapy, the chemotherapy is selected from the group consisting of carmustine, cisplatin, cyclophosphamide $\geqq$1500 mg/m^2, dacarbazine, dactinomycin, mechlorethamine, streptozotocin and combinations thereof.

60) (Previously Presented) The method of claim 52, wherein when said chemotherapy is moderately emetic chemotherapy, the chemotherapy is selected from the group consisting of carboplatin, cyclophosphamide <1500 mg/m^2, cytarabine >1 mg/m^2, daunorubicin,

doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, oxaliplatin and combinations thereof.

61) (Previously Presented) The method of claim 52, wherein said chemotherapy is selected from the group consisting of carboplatin, cyclophosphamide, cytarabine >1 mg/m^2, daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, carmustine, cisplatin, dacarbazine, dactinomycin, mechlorethamine, streptozotocin, oxaliplatin and combinations thereof.

62) (Previously Presented) The method of claim 53, wherein when said chemotherapy is highly emetic chemotherapy, the chemotherapy is selected from the group consisting of carmustine, cisplatin, cyclophosphamide ≧1500 mg/m^2, dacarbazine, dactinomycin, mechlorethamine, streptozotocin and combinations thereof.

63) (Previously Presented) The method of claim 53, wherein when said chemotherapy is moderately emetic chemotherapy, the chemotherapy is selected from the group consisting of carboplatin, cyclophosphamide <1500 mg/m^2, cytarabine >1 mg/m^2, daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, oxaliplatin and combinations thereof.

64) (Previously Presented) The method of claim 53, wherein said chemotherapy is selected from the group consisting of carboplatin, cyclophosphamide, cytarabine >1 mg/m^2, daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, carmustine, cisplatin, dacarbazine, dactinomycin, mechlorethamine, streptozotocin, oxaliplatin and combinations thereof.

65) (Previously Presented) The method of claim 55, wherein when said chemotherapy is highly emetic chemotherapy, the chemotherapy is selected from the group consisting of carmustine, cisplatin, cyclophosphamide ≧1500 mg/m^2, dacarbazine, dactinomycin, mechlorethamine, streptozotocin and combinations thereof.

66) (Previously Presented) The method of claim 55, wherein when said chemotherapy is moderately emetic chemotherapy, the chemotherapy is selected from the group consisting of carboplatin, cyclophosphamide <1500 mg/m^2, cytarabine >1 mg/m^2, daunorubicin,

doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, oxaliplatin and combinations thereof.

67) (Previously Presented) The method of claim 55, wherein said chemotherapy is selected from the group consisting of carboplatin, cyclophosphamide, cytarabine >1 mg/m^2, daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, carmustine, cisplatin, dacarbazine, dactinomycin, mechlorethamine, streptozotocin, oxaliplatin and combinations thereof.

68) (New) The method of claim 52, wherein said treatment of CINV is defined as no emetic episodes and no use of rescue medication following said chemotherapy.

69) (New) The method of claim 52, wherein:

a) said regimen comprises a single administration of netupitant or pharmaceutically acceptable salt thereof and a single administration of palonosetron or pharmaceutically acceptable salt thereof;

b) said netupitant or pharmaceutically acceptable salt thereof and said palonosetron or pharmaceutically acceptable salt thereof are administered concomitantly and prior to said chemotherapy, without administering a second dose of either for at least five days after said chemotherapy; and

c) said regimen is effective to treat said CINV for a five day period after said chemotherapy.

70) (New) The method of claim 52, wherein:

a) said treatment of CINV is defined as no emetic episodes and no use of rescue medication following said chemotherapy;

b) said regimen comprises a single administration of netupitant or pharmaceutically acceptable salt thereof and a single administration of palonosetron or pharmaceutically acceptable salt thereof;

c) said netupitant or pharmaceutically acceptable salt thereof and said palonosetron or pharmaceutically acceptable salt thereof are administered concomitantly and prior to said chemotherapy, without administering a second dose of either for at least five days after said chemotherapy; and

d) said regimen is effective to treat said CINV for a five day period after said chemotherapy.

71) (New) The method of claim 70, wherein:

a) said netupitant is administered orally as the free base in a dose of from about 200 mg to about 400 mg; and

b) said palonosetron is administered orally as palonosetron hydrochloride in a dose of from about 0.25 mg to about 0.75 mg based on the weight of the free base.

72) (New) The method of claim 70, wherein:

a) said netupitant is administered orally as the free base in a dose of about 300 mg;

b) said palonosetron is administered orally as palonosetron hydrochloride in a dose of about 0.50 mg based on the weight of the free base; and

c) said netupitant and palonosetron are administered as a single unit dosage form less than 2 hours prior to said chemotherapy.

73) (New) The method of claim 70, wherein:

a) said chemotherapy comprises moderately emetogenic chemotherapy;

b) said netupitant is administered orally as the free base in a dose of about 300 mg;

c) said palonosetron is administered orally as palonosetron hydrochloride in a dose of about 0.50 mg based on the weight of the free base;

d) said netupitant and palonosetron are administered as a combination unit dosage form less than 2 hours prior to said chemotherapy; and

e) said dexamethasone is administered in a dose of about 12 mg, in a dosage form independent of said combination unit dosage form, less than 2 hours prior to said chemotherapy.

74) (New) The method of claim 70, wherein:

a) said chemotherapy comprises highly emetogenic chemotherapy;

b) said netupitant is administered orally as the free base in a dose of about 300 mg;

c) said palonosetron is administered orally as palonosetron hydrochloride in a dose of about 0.50 mg based on the weight of the free base;

d) said netupitant and palonosetron are administered as a combination unit dosage form less than 2 hours prior to said chemotherapy;

e) said dexamethasone is administered in a dose of about 12 mg, in a dosage form independent of said combination unit dosage form, less than 2 hours prior to said chemotherapy; and

f) said dexamethasone is further administered in a dose of about 8 mg on days 2, 3 and 4 following said chemotherapy.

75) (New) The method of claim 70, wherein said netupitant occupies at least 70% of said patient's striatum NK1 receptors ninety-six hours after said administration.

76) (New) The method of claim 70, wherein:

a) said chemotherapy is highly emetogenic chemotherapy; and

b) said netupitant is effective to treat said CINV during the acute and delayed phases of said CINV.

77) (New) The method of claim 70, wherein:

a) said chemotherapy is highly emetogenic chemotherapy; and

b) said regimen is effective to prevent nausea or reduce the severity of nausea in said patient during the acute and delayed phases of said CINV.

78) (New) The method of claim 70, wherein:

a) said chemotherapy is moderately emetogenic chemotherapy; and

b) said regimen is effective to prevent nausea or reduce the severity of nausea in said patient during the acute and delayed phases of said CINV.

79) (New) The method of claim 70, wherein (3S)-3-[(3aS)-1-oxo-2,3,3a,4,5,6-hexahydro-1H-benzo[de]isoquinoline-2-yl]- -1-azoniabicyclo[2.2.2]octan-1-olate is substantially absent from said palonosetron.

80) (New) The method of claim 70, wherein said netupitant occupies at least 70% of said patient's striatum NK1 receptors ninety-six hours after said administration.

81) (New) The method of claim 70, wherein said chemotherapy comprises cisplatin.

82) (New) The method of claim 70, wherein said chemotherapy comprises carboplatin, cisplatin, oxaliplatin, or doxorubicin.

83) (New) The method of claim 70, wherein said chemotherapy comprises cyclophosphamide.

84) (New) The method of claim 72, wherein:

a) said chemotherapy is highly emetogenic chemotherapy; and

b) said netupitant is effective to treat said CINV during the acute and delayed phases of said CINV.

85) (New) The method of claim 72, wherein:

a) said chemotherapy is highly emetogenic chemotherapy; and

b) said regimen is effective to prevent nausea or reduce the severity of nausea in said patient during the acute and delayed phases of said CINV.

86) (New) The method of claim 72, wherein:

a) said chemotherapy is moderately emetogenic chemotherapy; and

b) said regimen is effective to prevent nausea or reduce the severity of nausea in said patient during the acute and delayed phases of said CINV.

87) (New) The method of claim 72, wherein said netupitant occupies at least 70% of said patient's striatum NK1 receptors ninety-six hours after said administration.

88) (New) The method of claim 72, wherein said chemotherapy comprises cisplatin.

89) (New) The method of claim 72, wherein said chemotherapy comprises carboplatin, cisplatin, oxaliplatin, or doxorubicin.

90) (New) The method of claim 72, wherein said chemotherapy comprises cyclophosphamide.

91) (New) The method of claim 53, wherein said treatment of CINV is defined as no emetic episodes and no use of rescue medication following said chemotherapy.

92) (New) The method of claim 53, wherein:

a) said regimen comprises a single administration of netupitant or pharmaceutically acceptable salt thereof, without administering a second dose for at least five days after said chemotherapy;

b) said chemotherapy comprises moderately emetogenic or highly emetogenic chemotherapy;

c) if said chemotherapy comprises moderately emetogenic chemotherapy, said regimen comprises a single administration of dexamethasone without administering a second dose for at least five days after said chemotherapy;

d) if said chemotherapy comprises highly emetogenic chemotherapy, said regimen comprises administering a first dose of dexamethasone on day one and a second dose of dexamethasone on two, three and four after said chemotherapy;

e) said netupitant or pharmaceutically acceptable salt thereof and said first dose of dexamethasone are administered prior to said chemotherapy;

f) said regimen is effective to treat said CINV for a five day period after said chemotherapy.

93) (New) The method of claim 53, wherein:

a) said treatment of CINV is defined as no emetic episodes and no use of rescue medication following said chemotherapy;

b) said regimen comprises a single administration of netupitant or pharmaceutically acceptable salt thereof, without administering a second dose for at least five days after said chemotherapy;

c) said chemotherapy comprises moderately emetogenic or highly emetogenic chemotherapy;

d) if said chemotherapy comprises moderately emetogenic chemotherapy, said regimen comprises a single administration of dexamethasone without administering a second dose for at least five days after said chemotherapy;

e) if said chemotherapy comprises highly emetogenic chemotherapy, said regimen comprises administering a first dose of dexamethasone on day one and a second dose of dexamethasone on two, three and four after said chemotherapy;

f) said netupitant or pharmaceutically acceptable salt thereof and said first dose of dexamethasone are administered prior to said chemotherapy;

g) said regimen is effective to treat said CINV for a five day period after said chemotherapy.

94) (New) The method of claim 86, wherein:

a) said chemotherapy comprises moderately emetogenic chemotherapy;

b) said netupitant is administered orally as the free base in a dose of about 300 mg less than 2 hours prior to said chemotherapy; and

c) said single administration of dexamethasone comprises about 12 mg, in a dosage form independent of said netupitant less than 2 hours prior to said chemotherapy.

95) (New) The method of claim 86, wherein:

a) said chemotherapy comprises highly emetogenic chemotherapy;

b) said netupitant is administered orally as the free base in a dose of about 300 mg less than 2 hours prior to said chemotherapy;

c) said first dose of dexamethasone comprises about 12 mg, in a dosage form independent of said netupitant, administered less than 2 hours prior to said chemotherapy; and

d) said second dose comprises about 8 mg of dexamethasone administered on days 2, 3 and 4 following said chemotherapy.

96) (New) The method of claim 86, wherein said netupitant occupies at least 70% of said patient's striatum NK1 receptors ninety-six hours after said administration.

97) (New) The method of claim 86, wherein said netupitant is effective to treat said CINV during the acute and delayed phases of said CINV.

98) (New) The method of claim 86, wherein said regimen is effective to prevent nausea in said patient following the administration of said chemotherapy.

99) (New) The method of claim 86, wherein said regimen is effective to reduce the severity of nausea in said patient following the administration of said chemotherapy.

100) (New) The method of claim 86, wherein said chemotherapy comprises cisplatin.

101) (New) The method of claim 86, wherein said chemotherapy comprises carboplatin, cisplatin, oxaliplatin, or doxorubicin.

102) (New) The method of claim 86, wherein said chemotherapy comprises cyclophosphamide.

103) (New) The method of claim 55, wherein said treatment of CINV is defined as no emetic episodes and no use of rescue medication following said chemotherapy.

104) (New) The method of claim 55, 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.

105) (New) The method of claim 55, 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.

106) (New) The method of claim 105, wherein said netupitant occupies at least 70% of said patient's striatum NK1 receptors ninety-six hours after said administration.

107) (New) The method of claim 105, 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.

108) (New) The method of claim 105, 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.

109) (New) The method of claim 105, 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.

110) (New) The method of claim 105, 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.

111) (New) The method of claim 105, wherein said chemotherapy comprises cisplatin.

112) (New) The method of claim 105, wherein said chemotherapy comprises carboplatin, cisplatin, oxaliplatin, or doxorubicin.

113) (New) The method of claim 105, wherein said chemotherapy comprises cyclophosphamide.

CONCLUSION

Applicant thanks for the Office for its diligent attention to this application, and remains available to discuss any outstanding issues. To the extent any fee is owed for this response, the Office is authorized to charge deposit account number 20-1507 of Customer No. 06980.

Respectfully submitted,

May 26, 2015

/Clark G. Sullivan/

TROUTMAN SANDERS LLP
875 Third Avenue
New York, NY 10022
(212) 704-6105
Customer No.: 06980

Clark G. Sullivan
Registration No. 36,942

Attorney Docket No.: 244168.000015US4

PTO/AIA/22 (03-13)
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PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)	Docket Number (Optional) 244168.000015US4
Application Number 14/069,927	Filed 11-01-2013
For COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING	
Art Unit 1629	Examiner Webb, Walter E.

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above-identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

		Fee	Small Entity Fee	Micro Entity Fee	
☐	One month (37 CFR 1.17(a)(1))	$200	$100	$50	$
☐	Two months (37 CFR 1.17(a)(2))	$600	$300	$150	$
☑	Three months (37 CFR 1.17(a)(3))	$1,400	$700	$350	$ 1,400
☐	Four months (37 CFR 1.17(a)(4))	$2,200	$1,100	$550	$
☐	Five months (37 CFR 1.17(a)(5))	$3,000	$1,500	$750	$

☐ Applicant asserts small entity status. See 37 CFR 1.27.

☐ Applicant certifies micro entity status. See 37 CFR 1.29.
Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously.

☐ A check in the amount of the fee is enclosed.

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

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

☑ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 201507.

☑ Payment made via EFS-Web.

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.

I am the

☐ applicant.

☑ attorney or agent of record. Registration number 36942.

☐ attorney or agent acting under 37 CFR 1.34. Registration number _____.

/Clark G. Sullivan/	May 26, 2015
Signature	Date
Clark G. Sullivan	212-704-6105
Typed or printed name	Telephone Number

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.

☐ * Total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.136(a). 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 6 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: Mail Stop PCT, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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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.

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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.

Electronic Patent Application Fee Transmittal

Application Number:	14069927
Filing Date:	01-Nov-2013
Title of Invention:	COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING
First Named Inventor/Applicant Name:	Fabio TRENTO
Filer:	Clark G. Sullivan/Dwight Peck
Attorney Docket Number:	244168.000015US4

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:				
Claims in Excess of 20	1202	42	80	3360
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Extension - 3 months with $0 paid	1253	1	1400	1400
Miscellaneous:				
			Total in USD ($)	**4760**

Electronic Acknowledgement Receipt

EFS ID:	22445722
Application Number:	14069927
International Application Number:	
Confirmation Number:	3207
Title of Invention:	COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING
First Named Inventor/Applicant Name:	Fabio TRENTO
Customer Number:	6980
Filer:	Clark G. Sullivan/Dwight Peck
Filer Authorized By:	Clark G. Sullivan
Attorney Docket Number:	244168.000015US4
Receipt Date:	26-MAY-2015
Filing Date:	01-NOV-2013
Time Stamp:	16:11:40
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$4760
RAM confirmation Number	3432
Deposit Account	201507
Authorized User	SULLIVAN, CLARK G.

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

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		PTO_Amendment_to_Non_Final_Office_Action.pdf	97000 ae9e91e0e5707d00a132743a0df43b0cba7f44bd	yes	13

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment/Req. Reconsideration-After Non-Final Reject	1	3
	Claims	4	12
	Applicant Arguments/Remarks Made in an Amendment	13	13

Warnings:

Information:

2	Extension of Time	PTO_EOT.pdf	97116 c2e0750d8bb7129949ab4f2fc967b1dcf19b25f5	no	2

Warnings:

Information:

3	Fee Worksheet (SB06)	fee-info.pdf	32865 7d488b96a8586d33509b6ad25f9710784e5692e7	no	2

Warnings:

Information:

Total Files Size (in bytes):	226981

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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.

PTO/SB/06 (09-11)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 14/069,927	Filing Date 11/01/2013	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT **05/26/2015**

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 62	Minus	** 20	= 42	X $80 =	3360
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	**3360**

AMENDMENT

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

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

LIE
/BURNELL L. ROSS/

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**
If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

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

PTO/AIA/82A (07-13)
Approved for use through 11/30/2014. OMB 0651-0051
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

TRANSMITTAL FOR POWER OF ATTORNEY TO ONE OR MORE REGISTERED PRACTITIONERS

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

Application Number	14/069,927
Filing Date	11-01-2013
First Named Inventor	Fabio TRENTO
Title	COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING
Art Unit	1612
Examiner Name	WEBB, WALTER E
Attorney Docket Number	244168.000015US4

SIGNATURE of Applicant or Patent Practitioner

Signature	/Clark G. Sullivan/	Date (Optional)	June 1, 2015
Name	Clark G. Sullivan	Registration Number	36,942
Title (if Applicant is a juristic entity)			
Applicant Name (if Applicant is a juristic entity)			

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

☑ *Total of 1 forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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

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

PTO/AIA/82B (07-13)
Approved for use through 11/30/2014. OMB 0651-0031
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
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POWER OF ATTORNEY BY APPLICANT

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

Application Number	Filing Date

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

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

OR

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

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

☑ The address associated with the above-mentioned Customer Number

OR

☐ The address associated with Customer Number:

OR

Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Email			

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

HELSINN HEALTHCARE SA

☐ Inventor or Joint Inventor (title not required below)

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

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

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

SIGNATURE of Applicant for Patent

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

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

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

☐ Total of forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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

Privacy Act Statement

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

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

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Acknowledgement Receipt

EFS ID:	22495214
Application Number:	14069927
International Application Number:	
Confirmation Number:	3207
Title of Invention:	COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING
First Named Inventor/Applicant Name:	Fabio TRENTO
Customer Number:	6980
Filer:	Clark G. Sullivan/Dwight Peck
Filer Authorized By:	Clark G. Sullivan
Attorney Docket Number:	244168.000015US4
Receipt Date:	01-JUN-2015
Filing Date:	01-NOV-2013
Time Stamp:	12:54:38
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Power of Attorney	PTO-244168-000015US4-POA-AIA82A.pdf	1085443 dfc9523b6c313610bebcae047b8572ca11fa0dc8	no	3

Warnings:	
Information:	

Total Files Size (in bytes):	1085443

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

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

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

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

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
14/069,927	11/01/2013	Fabio TRENTO	244168.000015US4

CONFIRMATION NO. 3207

POA ACCEPTANCE LETTER

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

OC00000075527769

Date Mailed: 06/04/2015

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 06/01/2015.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/dtdinh/

Doc Code: DIST.E.FILE Document Description: Electronic Terminal Disclaimer - Filed	PTO/SB/25 PTO/SB/26 U.S. Patent and Trademark Office Department of Commerce

Electronic Petition Request	**TERMINAL DISCLAIMER TO OBVIATE A PROVISIONAL DOUBLE PATENTING REJECTION OVER A PENDING "REFERENCE" APPLICATION AND TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A "PRIOR" PATENT**
Application Number	14069927
Filing Date	01-Nov-2013
First Named Inventor	Fabio TRENTO
Attorney Docket Number	244168.000015US4
Title of Invention	COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING

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

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

Owner	Percent Interest
HELSINN HEALTHCARE SA	100 %

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

14069970 filed on 11/01/2013

as the term of any patent granted on said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending reference application. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and any patent granted on the reference application are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term of any patent granted on said reference application, "as the term of any patent granted on said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending reference application," in the event that any such patent granted on the pending reference application: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321, has all claims canceled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as shortened by any terminal disclaimer filed prior to its grant.

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

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8623826

as the term of said prior patent is presently shortened by any terminal disclaimer. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the prior patent are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of the term of any patent granted on the instant application that would extend to the expiration date of the full statutory term of the prior patent, "as the term of said prior patent is presently shortened by any terminal disclaimer," in the event that said prior patent later:
- expires for failure to pay a maintenance fee;
- is held unenforceable;
- is found invalid by a court of competent jurisdiction;
- is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321;
- has all claims canceled by a reexamination certificate;
- is reissued; or
- is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

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

○ I certify, in accordance with 37 CFR 1.4(d)(4), that the terminal disclaimer fee under 37 CFR 1.20(d) required for this terminal disclaimer has already been paid in the above-identified application.

Applicants claims the following fee status:

○ Small Entity

○ Micro Entity

◉ Regular Undiscounted

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

THIS PORTION MUST BE COMPLETED BY THE SIGNATORY OR SIGNATORIES

I certify, in accordance with 37 CFR 1.4(d)(4) that I am:

◉ An attorney or agent registered to practice before the Patent and Trademark Office who is of record in this application

Registration Number 36942

○ A sole inventor

○ A joint inventor; I certify that I am authorized to sign this submission on behalf of all of the inventors as evidenced by the power of attorney in the application

○ A joint inventor; all of whom are signing this request

Signature	/Clark G. Sullivan/
Name	Clark G. Sullivan

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

Electronic Patent Application Fee Transmittal

Application Number:	14069927
Filing Date:	01-Nov-2013
Title of Invention:	COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING
First Named Inventor/Applicant Name:	Fabio TRENTO
Filer:	Clark G. Sullivan/Dwight Peck
Attorney Docket Number:	244168.000015US4

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Statutory or Terminal Disclaimer	1814	1	160	160
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**160**

Doc Code: DISQ.E.FILE
Document Description: Electronic Terminal Disclaimer – Approved

Application No.: 14069927

Filing Date: 01-Nov-2013

Applicant/Patent under Reexamination: TRENTO et al.

Electronic Terminal Disclaimer filed on June 5, 2015

☒ APPROVED

This patent is subject to a terminal disclaimer

☐ DISAPPROVED

Approved/Disapproved by: Electronic Terminal Disclaimer automatically approved by EFS-Web

U.S. Patent and Trademark Office

Electronic Acknowledgement Receipt

EFS ID:	22550571
Application Number:	14069927
International Application Number:	
Confirmation Number:	3207
Title of Invention:	COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING
First Named Inventor/Applicant Name:	Fabio TRENTO
Customer Number:	6980
Filer:	Clark G. Sullivan/Dwight Peck
Filer Authorized By:	Clark G. Sullivan
Attorney Docket Number:	244168.000015US4
Receipt Date:	05-JUN-2015
Filing Date:	01-NOV-2013
Time Stamp:	14:37:40
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$160
RAM confirmation Number	847
Deposit Account	201507
Authorized User	SULLIVAN, CLARK G.

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

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Electronic Terminal Disclaimer-Filed	eTerminal-Disclaimer.pdf	36316 04443559afbff194cc6f4f95c43060006c52f23d	no	3
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30787 af3fd4c622b23121cb31a0fcc754b08770164389	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	67103		

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

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

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

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

UNITED STATES PATENT AND TRADEMARK OFFICE

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

NOTICE OF ALLOWANCE AND FEE(S) DUE

6980 7590 07/28/2015

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

EXAMINER
WEBB, WALTER E

ART UNIT	PAPER NUMBER
1612	

DATE MAILED: 07/28/2015

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/069,927	11/01/2013	Fabio TRENTO	244168.000015US4	3207

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	10/28/2015

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)

6980 7590 07/28/2015
TROUTMAN SANDERS LLP
600 Peachtree Street
Suite 5200
Atlanta, GA 30308

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

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

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/069,927	11/01/2013	Fabio TRENTO	244168.000015US4	3207

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	10/28/2015

EXAMINER	ART UNIT	CLASS-SUBCLASS
WEBB, WALTER E	1612	514-017700

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
- ❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.
1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:
- ❑ Issue Fee
- ❑ Publication Fee (No small entity discount permitted)
- ❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
- ❑ A check is enclosed.
- ❑ Payment by credit card. Form PTO-2038 is attached.
- ❑ The director is hereby authorized to charge the required fee(s), any deficiency, or 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
  NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
- ❑ Applicant asserting small entity status. See 37 CFR 1.27
  NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
- ❑ Applicant changing to regular undiscounted fee status.
  NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

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

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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14/069,927	11/01/2013	Fabio TRENTO	244168.000015US4	3207

6980 7590 07/28/2015

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

EXAMINER	
WEBB, WALTER E	

ART UNIT	PAPER NUMBER
1612	

DATE MAILED: 07/28/2015

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.
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. 14/069,927	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 *TD approval filed 6/5/2015*.
   ☐ 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 *52-113*. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov .
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

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

   * Certified copies not received: _____.

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

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

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 1/15/2015
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
5. ☐ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/WALTER WEBB/
Primary Examiner, Art Unit 1612

EAST Search History

EAST Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L2	22368	nausea or vomiting or emesis	USPAT; UPAD	OR	ON	2015/07/21 14:57
L3	395	palonosetron or netupitant	USPAT; UPAD	OR	ON	2015/07/21 14:57
L4	222	l2 and l3	USPAT; UPAD	OR	ON	2015/07/21 14:57
L5	0	l4 and palonestron	USPAT; UPAD	OR	ON	2015/07/21 14:58
L6	7	l4 and netupitant	USPAT; UPAD	OR	ON	2015/07/21 14:58
L7	1	l4 and palonostron	USPAT; UPAD	OR	ON	2015/07/21 14:59
L8	220	l4 and palonosetron	USPAT; UPAD	OR	ON	2015/07/21 15:00
L9	5	l8 and netupitant	USPAT; UPAD	OR	ON	2015/07/21 15:00

7/21/2015 3:01:40 PM
C:\Users\wwebb\Documents\EAST\Workspaces\14069927_Method of treating nausea vomiting with palonosetron and netupitant.wsp

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14069927	TRENTO ET AL.
	Examiner	Art Unit
	WALTER WEBB	1612

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

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

CLAIM		DATE								
Final	Original	11/28/2014	07/21/2015							
	1	-	-							
	2	-	-							
	3	-	-							
	4	-	-							
	5	-	-							
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	34	-	-							
	35	-	-							
	36	-	-							

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CLAIM		DATE								
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15	66	✓	=							
16	67	✓	=							
17	68		=							
18	69		=							
19	70		=							
20	71		=							
21	72		=							

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
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	Examiner	Art Unit
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☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☒ T.D. ☐ R.1.47

CLAIM		DATE								
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55	106		=							
56	107		=							
57	108		=							

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14069927	TRENTO ET AL.
	Examiner	**Art Unit**
	WALTER WEBB	1612

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

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

CLAIM		DATE								
Final	Original	11/28/2014	07/21/2015							
58	109		=							
59	110		=							
60	111		=							
61	112		=							
62	113		=							

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14069927	TRENTO ET AL.
	Examiner	**Art Unit**
	WALTER WEBB	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)	62	
/WALTER WEBB/ Primary Examiner.Art Unit 1612	07/21/2015	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	Claim 1	None

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14069927	TRENTO ET AL.
	Examiner	**Art Unit**
	WALTER WEBB	1612

US ORIGINAL CLASSIFICATION		INTERNATIONAL CLASSIFICATION												
CLASS	SUBCLASS	CLAIMED					NON-CLAIMED							
514	17.7	A	6	1	K	31 / 496 (2006.01.01)								
CROSS REFERENCE(S)		A	6	1	K	31 / 573 (2006.01.01)								
		A	6	1	K	31 / 473 (2006.01.01)								
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)													
514	171	253.01	183	185	188									

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	62	
/WALTER WEBB/ Primary Examiner.Art Unit 1612	07/21/2015	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	Claim 1	None

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

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Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	52	17	68	33	84	49	100								
2	53	18	69	34	85	50	101								
3	54	19	70	35	86	51	102								
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8	59	24	75	40	91	56	107								
9	60	25	76	41	92	57	108								
10	61	26	77	42	93	58	109								
11	62	27	78	43	94	59	110								
12	63	28	79	44	95	60	111								
13	64	29	80	45	96	61	112								
14	65	30	81	46	97	62	113								
15	66	31	82	47	98										
16	67	32	83	48	99										

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 62	
/WALTER WEBB/ Primary Examiner.Art Unit 1612 (Primary Examiner)	07/21/2015 (Date)	O.G. Print Claim(s) Claim 1	O.G. Print Figure None

UNITED STATES PATENT AND TRADEMARK OFFICE

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BIB DATA SHEET

CONFIRMATION NO. 3207

SERIAL NUMBER	FILING or 371(c) DATE RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
14/069,927	11/01/2013	514	1612	244168.000015US4

APPLICANTS

Helsinn Healthcare S.A., 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 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 ****

11/18/2013

Foreign Priority claimed ☐ Yes ☑ No 35 USC 119(a-d) conditions met ☐ Yes ☑ No Verified and Acknowledged /WALTER E WEBB/ Examiner's Signature	☐ Met after Allowance Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		ITALY	5	16	3

ADDRESS

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

TITLE

COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING

FILING FEE RECEIVED		
5100	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

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Receipt date: 01/15/2015

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	14069927
Filing Date	2013-11-01
First Named Inventor	Fabio TRENTO
Art Unit	1612
Examiner Name	Walter E. WEBB
Attorney Docket Number	244168.000015US4

U.S.PATENTS

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

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U.S.PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

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FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	2009-507933	JP		2009-02-26	Helsinn Healthcare S.A.	Corresponds to WO 2008049552 (previously cited).	☒

If you wish to add additional Foreign Patent Document citation information please click the Add button

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /W.W./

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99) Receipt date: 01/15/2015		
	Application Number	14069927
	Filing Date	2013-11-01
	First Named Inventor	Fabio TRENTO
	Art Unit	1612
	Examiner Name	Walter E. WEBB
	Attorney Docket Number	244168.000015US4

	1	Japanese Office Action dated November 19, 2014, which issued during prosecution of Japanese Patent Application No. 2012-539433.	☒
	2	Torsten HOFFMANN, et al., "Design and synthesis of a novel, achiral class of highly potent and selective, orally active neurokinin-1 receoptor antagonists", Bioorganic & Medicinal Chemistry Letters 16 (2006) 1362-1365.	☐

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

EXAMINER SIGNATURE

Examiner Signature	/Walter Webb/	Date Considered	07/21/2015

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

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

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /W.W./

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14069927	TRENTO ET AL.
	Examiner	Art Unit
	WALTER WEBB	1612

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner
514	17.7	11/21/2014	WW

SEARCH NOTES		
Search Notes	Date	Examiner
Inventor Name Search on PALM	11/21/2014	WW
EAST Search History	11/21/2014	WW
NPL Search Terms: netupitant palonosetron	11/21/2014	WW

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
514	17.7, 171, 252.03	7/21/2015	WW

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)

6980 7590 07/28/2015
TROUTMAN SANDERS LLP
600 Peachtree Street
Suite 5200
Atlanta, GA 30308

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

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

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/069,927	11/01/2013	Fabio TRENTO	244168.000015US4	3207

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	10/28/2015

EXAMINER	ART UNIT	CLASS-SUBCLASS
WEBB, WALTER E	1612	514-017700

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
- ☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 TROUTMAN SANDERS LLP
2
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: HELSINN HEALTHCARE SA

(B) RESIDENCE: (CITY and STATE OR COUNTRY): LUGANO/PAZZALLO, SWITZERLAND

Please check the appropriate assignee category or categories (will not be printed on the patent): ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:
- ☒ Issue Fee
- ☐ Publication Fee (No small entity discount permitted)
- ☐ Advance Order - # of Copies .....

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
- ☐ A check is enclosed.
- ☐ Payment by credit card. Form PTO-2038 is attached.
- ☒ The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number 20-1507 (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
- ☐ Applicant certifying micro entity status. See 37 CFR 1.29 — NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
- ☐ Applicant asserting small entity status. See 37 CFR 1.27 — NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
- ☐ Applicant changing to regular undiscounted fee status. — NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

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

Authorized Signature /Kenneth Ma 63,839/ Date October 12, 2015

Typed or printed name KENNETH MA Registration No. 63,839

Electronic Patent Application Fee Transmittal

Application Number:	14069927
Filing Date:	01-Nov-2013
Title of Invention:	COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING
First Named Inventor/Applicant Name:	Fabio TRENTO
Filer:	Kenneth B. Ma/Dwight Peck
Attorney Docket Number:	244168.000015US4

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:				
Utility Appl Issue Fee	1501	1	960	960

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**960**

Electronic Acknowledgement Receipt

EFS ID:	23752944
Application Number:	14069927
International Application Number:	
Confirmation Number:	3207
Title of Invention:	COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING
First Named Inventor/Applicant Name:	Fabio TRENTO
Customer Number:	6980
Filer:	Kenneth B. Ma/Dwight Peck
Filer Authorized By:	Kenneth B. Ma
Attorney Docket Number:	244168.000015US4
Receipt Date:	12-OCT-2015
Filing Date:	01-NOV-2013
Time Stamp:	12:33:01
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$960
RAM confirmation Number	8875
Deposit Account	201507
Authorized User	MA, KENNETH

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

Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Issue Fee Payment (PTO-85B)	issuefee.pdf	366368 38b4da13f16f253d8ae4c961e3ac0783fc04bff0	no	1
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	31059 fb38ad0c255eb4c41c588739479df19426d132d5	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	397427		

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

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

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

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

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/069,927	11/17/2015	9186357	244168.000015US4	3207

6980 7590 10/28/2015

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

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

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

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

Helsinn Healthcare S.A., Lugano/Pazzallo, SWITZERLAND;
Fabio TRENTO, Pare, ITALY;
Sergio CANTOREGGI, Cagiallo, SWITZERLAND;
Giorgia ROSSI, Cernobbio, ITALY;
Roberta CANNELLA, Varese, ITALY;
Daniele BONADEO, Casalzuigno, ITALY;

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The USA offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to encourage and facilitate business investment. To learn more about why the USA is the best country in the world to develop technology, manufacture products, and grow your business, visit SelectUSA.gov.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re: U.S. Patent No. 9,186,357 B1

Issued: November 17, 2015

To: Fabio TRENTO et al.

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

RECEIVED
JUN 12 2018
PATENT EXTENSION
OPLA

EXPRESS MAIL: EE 182390395

Mail Stop Hatch-Waxman PTE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL LETTER FOR PATENT TERM EXTENSION APPLICATION

Dear Sir:

Attached in triplicate is an Application for Extension of Patent Term of U.S. Patent No. 9,186,357 B1 under 35 U.S.C. § 156. A check in the amount of $1,120 is also enclosed as prescribed in 37 C.F.R. § 1.20(j). The Commissioner is authorized to charge any additional fees in connection with the filing of this Application to Deposit Account No. 600254.

Applicant can be reached through its undersigned attorney by telephone at (404) 483-9360. All correspondence should be directed to the address given below.

JUNE 12, 2018

Respectfully submitted,

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

Sullivan IP Solutions
PO Box 2252
New York NY 10163
404.483.9360

Customer No. 140619

Attachments: Three copies of Application for Extension of Patent Term under 35 U.S.C. § 156 (including Appendices A-E)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re: U.S. Patent No. 9,186,357 B1

Issued: November 17, 2015

To: Fabio TRENTO et al.

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

EXPRESS MAIL: EE 182390395

Mail Stop Hatch-Waxman PTE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RECEIVED
JUN 12 2018
PATENT EXTENSION
OPLA

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156

Dear Sir:

Applicant, Helsinn Healthcare SA ("Helsinn"), a company organized and existing under the laws of the Swiss Confederation, represents that it is the owner of the entire title and interest in and to U.S. Patent No. 9,186,357 B1 (sometimes "the '357 patent), by virtue of the Assignment recorded on February 4, 2015, at Reel 034886, Frame 0944. Extension of the term of the '357 patent under 35 U.S.C. § 156 is hereby respectfully requested. The following information is submitted in accordance with 35 U.S.C. § 156(d) and 37 C.F.R. § 1.740, and follows the format and requirements set forth in 37 C.F.R. § 1.740.

By the Power of Attorney attached hereto as "Appendix A", Applicant appoints attorneys associated with Customer No. 140619 for this application for extension of patent term and to transact all business in the U.S. Patent and Trademark Office in connection therewith.

The following Appendices are attached hereto:

Appendix A:	Power of Attorney
Appendix B:	FDA-approved labeling for Akynzeo™ for injection.
Appendix C:	FDA April 19, 2018 Approval Letter for NDA 210493
Appendix D:	U.S. Patent No. 9,186,357 B1
Appendix E:	Chronology of Significant Regulatory Events

REQUIREMENTS UNDER 37 C.F.R. § 1.740

(1) "A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics;" 37 C.F.R. §1.740(a)(1).

The approved product is Akynzeo™ for injection. Akynzeo™ for injection is a lyophilized powder in a single-dose vial for reconstitution. The product contains two active ingredients, fosnetupitant and palonosetron, in amounts equivalent to 235 mg base and 0.25 mg base, respectively. The fosnetupitant is present as the chloride hydrochloride salt; the palonosetron is present as the hydrochloride salt.

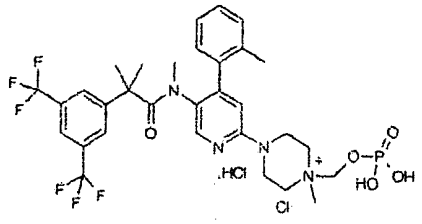
Fosnetupitant chloride hydrochloride:

Chemical name: 2-(3,5-bis-trifluoro-methylphenyl)-N-methyl-N-[6-(4-methyl-4-O-methylene phosphate-piperazinium-1-yl)- 4-o-tolyl-pyridin-3-yl]-isobutyramide chloride hydrochloride.

Empirical formula: $C_{31}H_{36}F_6N_4O_5P \cdot Cl \cdot HCl$.

Molecular weight: 761.53.

Chemical Structure:



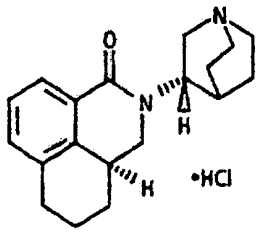
Palonosetron hydrochloride:

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

Empirical formula: $C_{19}H_{24}N_2O \cdot HCl$.

Molecular weight: 332.87.

Chemical Structure:



A copy of the prescribing information for Akynzeo™ for injection is attached in Appendix B.

(2) "A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred;" 37 C.F.R. § 1.740(a)(2).

Akynzeo™ for injection was reviewed under Section 505 of the Federal Food, Drug, and Cosmetic Act (FFDC Act), 21 U.S.C. § 355. The IND for the product was reviewed under section 505(i) of the FFDC Act (21 U.S.C. § 355(i)); the NDA was reviewed under section 505(b) of the FFDC Act (21 U.S.C. § 355(b)).

(3) "An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred;" 37 C.F.R. § 1.740(a)(3).

Akynzeo™ for injection received approval for commercial marketing or use under Section 505 of the FFDC Act, 21 U.S.C. § 355, on April 19, 2018, under NDA 210493. A copy of the April 19, 2018, approval letter is attached in Appendix C.

(4) "In the case of a drug product, an identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act, or a statement of when the active ingredient was approved for commercial marketing or use (either alone or in combination

with other active ingredients), the use for which it was approved, and the provision of law under which it was approved." 37 C.F.R. § 1.740(a)(4).

Fosnetupitant has not previously been approved for commercial marketing or use under the FFDC Federal Food, Drug and Cosmetic Act, the Public Health Service Act or the Virus-Serum-Toxin Act.

Palonosetron was first approved under Section 505 of the FFDC Act in Aloxi™ intravenous solution under NDA 021372, on July 25, 2003, for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy; and the prevention of acute nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy.

Palonosetron was also approved under Section 505 of the FFDC Act in Aloxi™ oral capsules under NDA 022233, on August 22, 2008, for the prevention of acute nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy.

Palonosetron in combination with netupitant was also approved under Section 505 of the FFDC Act in Akynzeo™ oral capsules under NDA 205718, on October 10, 2014, for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy.

(5) "A statement that the application is being submitted within the sixty day period permitted for submission pursuant to § 1.720(1) and an identification of the last day on which the application could be submitted;" 37 C.F.R. § 1.740(a)(5)

This application is being submitted within the sixty-day period following FDA approval of the NDA for Akynzeo™ for injection. FDA approved the NDA for Akynzeo™ for

injection on April 19, 2018. The sixty-day period for submission of this application will expire on June 18, 2018.

(6) "A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration;" 37 C.F.R. § 1.740(a)(6).

Inventors:	Fabio TRENTO
	Sergio CANTOREGGI
	Giorgia ROSSI
	Roberta CANNELLA
	Daniele BONADEO
U.S. Patent No.:	9,186,357 B1
Issue date:	November 17, 2015
Expiration date:	November 18, 2030

(7) "A copy of the patent for which an extension is being sought, including the entire specification (including claims) and drawings;" 37 C.F.R. § 1.740(a)(7).

A copy of U.S. Patent No. 9,186,357 B1 is attached as Appendix D.

(8) "A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or re-examination certificate issued in the patent," 37 C.F.R. § 1.740(a)(8).

U.S. Patent No. 9,186,357 B1 issued on November 17, 2015. Maintenance fees are not due until May 17, 2019.

No disclaimer, certificate of correction or re-examination certificate has issued to date in connection with U.S. Patent No. 9,186,357 B1.

(9) "A statement that the patent claims the approved product or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which one such patent claim reads on:

(i) The approved product if the listed claims include any claim to the approved product;

(ii) The method of using the approved product, if the listed claims include any claim to the method of using the approved product; and

(iii) The method of manufacturing the approved product, if the listed claims include any claim to the method of manufacturing the approved product;" 37 C.F.R. § 1.740(a)(9).

U.S. Patent No. 9,186,357 B1 claims a method of using Akynzeo™ for injection for the use approved by NDA 210493, i.e., "in combination with dexamethasone in adults for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy."

The applicable patent claims are 4, 14, 16, 52, 53, 54, 55, 56, 58, 60, 61, and 62, reproduced below in Table 1:

Table 1

Claim	Text
4	A method of treating chemotherapy induced nausea and vomiting (CINV) comprising inducing in a subject receiving chemotherapy blood levels of palonosetron and netupitant effective to treat said CINV.
14	The method of claim 4, wherein when said chemotherapy is highly emetic chemotherapy, the chemotherapy is selected from the group consisting of carmustine, cisplatin, cyclophosphamide $\geq$ 1500 mg/m^2, dacarbazine, dactinomycin, mechlorethamine, streptozotocin and combinations thereof.

16	The method of claim 4, wherein said chemotherapy is selected from the group consisting of carboplatin, cyclophosphamide, cytarabine > 1 mg/m^2, daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, carmustine, cisplatin, dacarbazine, dactinomycin, mechlorethamine, streptozotocin, oxaliplatin and combinations thereof.
52	The method of claim 4, wherein said treatment of CINV is defined as no emetic episodes and no use of rescue medication following said chemotherapy.
53	The method of claim 4, 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.
54	The method of claim 4, 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.
55	The method of claim 54, wherein said netupitant occupies at least 70% of said patient's striatum NK1 receptors ninety-six hours after said administration.
56	The method of claim 54, 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.
58	The method of claim 54, 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.
60	The method of claim 54, wherein said chemotherapy comprises cisplatin.
61	The method of claim 54, wherein said chemotherapy comprises carboplatin, cisplatin, oxaliplatin, or doxorubicin.
62	The method of claim 54, wherein said chemotherapy comprises cyclophosphamide.

Claim 4 reads on the FDA-approved method of using Akynzeo™ for injection for the following reasons:

1. Claim 4 recites:

"A method of treating chemotherapy induced nausea and vomiting (CINV) comprising inducing in a subject receiving chemotherapy blood levels of palonosetron and netupitant effective to treat said CINV."

2. Akynzeo™ for injection is indicated for "treating chemotherapy induced nausea and vomiting (CINV)" as recited in Claim 4. The FDA-approved prescribing information for Akynzeo™ for injection (Appendix B) states in the Indications and Usage Section 1:

"AKYNZEO for injection is indicated in combination with dexamethasone in adults for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy."

3. The '357 patent describes what is meant by inducing levels of netupitant in the bloodstream effective to treat CINV in column 10, lines 22-29[1]:

[1] 35 U.S.C. § 156(a) states that the '357 patent is eligible for a patent term extension if it "claims" "a method of using a product" that has been subject to a regulatory review period before its commercial marketing or use. The written description in the '357 patent at column 10, lines 22-29 proves that the '357 patent claims an approved method of using Akynzeo™ for injection because it proves "the subject matter which the applicant regards as his invention." See Hoechst-Roussel Pharm., Inc. v. Lehman, 109 F.3d 756, 758 (Fed. Cir. 1997) (explaining what is meant to "claim" an invention by reference to the text of 35 U.S.C. § 112). This written description also is what distinguishes the '357 patent from the patent involved in Angiotech Pharm. Inc. v. Lee, 191 F. Supp. 3d 509 (E.D. Va. 2016), which made no reference to the device actually approved by FDA.

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

4. The FDA-approved prescribing information for Akynzeo for injection (Appendix B) confirms that fosnetupitant is a prodrug of netupitant, and that Akynzeo™ for injection treats CINV by inducing levels of netupitant in the bloodstream effective to treat the CINV, stating:

Indications and Usage Section 1: "AKYNZEO for injection is a combination of palonosetron and fosnetupitant, a prodrug of netupitant: palonosetron prevents nausea and vomiting during the acute phase and fosnetupitant prevents nausea and vomiting during both the acute and delayed phase after cancer chemotherapy."

Pharmacokinetics Section 12.3 (Fosnetupitant / Metabolism): "Fosnetupitant is converted in vivo to netupitant by metabolic hydrolysis. In patients receiving AKYNZEO intravenously, netupitant exposure was 17-fold fosnetupitant exposure, as determined by their AUC_{inf} ratio."

(10) A statement, beginning on a new page of the relevant dates and information pursuant to 35 U.S.C. § 156(g) in order to enable the Secretary of Health and Human Services, or the Secretary of Agriculture, as appropriate, to determine the applicable regulatory review period as follows:

(i) For a patent claiming a human drug, antibiotic or human biological product:

(A) The effective date of the investigational new drug (IND) application and the IND number;

(B) The date on which a new drug application (NDA) ... was initially submitted and the NDA or PLA number ... and

(C) The date on which the NDA was approved or the Product License issued; 37 C.F.R. § 1.740(a)(10)(i).

In order to enable the Secretary to determine the applicable regulatory review period, the following information is provided:

(a) Helsinn's Investigational New Drug (IND) application for Akynzeo™ for injection (IND 115191) became effective on July 25, 2015;

(b) Helsinn Healthcare SA initially submitted a New Drug Application (NDA) for Akynzeo™ to the FDA, via electronic submission, on April 20, 2017 (NDA 210493); and

(c) FDA approved Helsinn's NDA 210493 for Akynzeo™ for injection on April 19, 2018.

(11) "A brief description beginning on a new page of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities;" 37 C.F.R. § 1.740(a)(11).

A brief description of the significant activities undertaken by Helsinn during the regulatory review period for Akynzeo™ for injection, and the significant dates applicable to such activities, is included in Appendix E hereto.

(12) "A statement beginning on a new page that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of the extension claimed, including how the length of extension was determined;" 37 C.F.R. § 1.740(a)(12).

Statement of Eligibility of the Patent for Extension

Applicant is of the opinion that U.S. Patent No. 9,186,357 B1 is eligible for an extension. This opinion is based on the following information on U.S. Patent No. 9,186,357 B1:

(a) 35 U.S.C. § 156(a): U.S. Patent No. 9,186,357 B1 claims the approved human drug product Akynzeo™ for injection.

(b) 35 U.S.C. § 156(a)(l): The term of the '357 patent has not expired prior to the submission of this application.

(c) 35 U.S.C. § 156(a)(2): The term of the '357 patent has never been previously extended under 35 U.S.C. § 156(e)(l).

(d) This application for extension is in compliance with 37 C.F.R. § 1.740.

(e) 35 U.S.C. § 156(a)(4): The product, Akynzeo™ for injection, has been subject to a regulatory review period as defined in 35 U.S.C. § 156(g) before its commercial marketing or use.

(f) 35 U.S.C. § 156(a)(5)(A): The NDA for the product received approval under the provision of law (i.e., FFDC Act § 505) under which the applicable regulatory review occurred.

(g) 35 U.S.C. § 156(d)(1): This application was submitted within sixty (60) days from the April 19, 2018 NDA approval date.

(h) 35 U.S.C. § 156(c)(4): No other patent term has been extended for the same regulatory review period for this product.

Statement as to Length of Extension Claimed

The term of U.S. Patent No. 9,186,357 B1 should be extended by 519 days, or until April 19, 2032. This term of extension was determined on the following bases.

(a) The regulatory review period under 35 U.S.C. § 156(g)(1)(B) equals the sum of the following periods (i) and (ii)

(i) The time between the date an exemption under section 505(i) of the FFDCA became effective (the effective date of the IND) and the date an application was initially submitted under section 505 of the FFDCA (the date of the initial submission of the NDA).

and

(ii) The time between the date an application was initially submitted under section 505(b) of the FFDCA (the date of the initial submission of the NDA) and the date the application was approved (the approval date of the NDA).

An IND for the product became effective on July 25, 2015. The NDA for the product was submitted on April 20, 2017. Thus, for the purpose of this calculation, item (i) equals the number of days from July 25, 2015, to April 20, 2017, or 635 days.

The NDA for the product was submitted on April 20, 2017. The NDA was approved on April 19, 2018. Thus, for the purpose of this calculation, item (ii) equals the number of days from April 20, 2017, to April 19, 2018, or 364 days.

(b) In accordance with 35 U.S.C. § 156(c), the term of a patent eligible for extension shall be extended by the time equal to the regulatory review period for the approved product which occurred after the date the patent issued. Because U.S. Patent No. 9,186,357 B1 issued on November 17, 2015, which is after the effective

date of the IND, period (i) must be reduced to the period between November 17, 2015 and the NDA filing date (April 20, 2017). Therefore, period (i) must be reduced to 520 days. The entire regulatory review period calculated for item (ii) occurred after the issuance date of the patent. Therefore, period (ii) remains 364 days.

(c) 35 U.S.C. § 156(c)(1) requires that each period be reduced by any period during which the applicant did not act with due diligence. There has been no lack of due diligence during the period of regulatory review. Accordingly, no reduction in the review period is required by this provision.

(d) 35 U.S.C. § 156(c)(2) requires that each period include only one-half of the number of days in phase (i). One-half of the number of days in phase (i) equals one-half of 520 days, or 260 days. Adding this number of days to the number of days in phase (ii) (364 days) results in a review period of 624 days.

(e) 35 U.S.C. § 156(c)(3) requires that, if the period remaining in the patent term after the date of approval of the approved product when added to the regulatory review period as revised under paragraphs (c) and (d) above exceeds fourteen years, the period of extension shall be reduced so that the sum of both such periods does not exceed fourteen years. Because the number of days between November 17, 2030 (the expiration date of the patent) and April 19, 2032 (14 years from NDA approval) is 519 days, which is less than the 624 days calculated in paragraphs (c) and (d), the period of extension must be reduced to 519 days, or April 19, 2032.

(f) 35 U.S.C. §156(g)(6) limits the period of patent term extension to a maximum of five years from the original expiration date of the patent. The original expiration date of U.S. Patent No. 9,186,357 B1 is November 17, 2030. Accordingly, the maximum extension allowed by this provision would extend the term to November 17, 2035. Extension of the patent by the number of days calculated in paragraph (5)

(519 days) would not extend the patent beyond this date. Accordingly, this provision does not operate to shorten the period of extension to which U.S. Patent No. 9,186,357 B1is entitled.

Thus, U.S. Patent No. 9,186,357 B1 is entitled to an extension of 519 days to April 19, 2032.

(13) "A statement that applicant acknowledges a duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought;" 37 C.F.R. § 1.740(a)(13).

Applicant acknowledges a duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to any determination of entitlement to the extension sought.

(14) "The prescribed fee for receiving and acting upon the application for extension (see §1.20(j));" 37 C.F.R. § 1.740(a)(14).

Pursuant to 37 C.F.R. § 1.20(j), a check in the amount of $1,120.00 is enclosed with this application. Should additional fees be necessary in connection with the filing of this paper, or if a petition for extension of time is required for timely acceptance of same, the Director is hereby authorized to charge Deposit Account No. 600254 for any such fees.

(15) "The name, address and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed;" 37 C.F.R. § 1.740(a)(15).

Please direct all inquiries and correspondence relating to this application for term extension to:

Clark G. Sullivan
Sullivan IP Solutions
PO Box 2252
New York NY 10163
404.483.9360

(16) "The application under this section must be accompanied by two additional copies of such application (for a total of three copies)." 37 C.F.R. § 1.740(b).

This application for patent extension, including its attachments, is being submitted as one original and two duplicate copies thereof.

CONCLUSION

WHEREFORE, a certificate of correction extending the term of U.S. Patent No. 9,186,357 B1 for a period of 519 days to April 19, 2032, is earnestly solicited.

Respectfully submitted,

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

June 12, 2018

Sullivan IP Solutions
PO Box 2252
New York NY 10163
404.483.9360

Customer No. 140619

APPENDIX A

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

PTO/AIA/82A (07-13)
Approved for use through 01/31/2018. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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NOTE: This form is to be submitted with the Power of Attorney by Applicant form (PTO/AIA/82B) to identify the application to which the Power of Attorney is directed, in accordance with 37 CFR 1.5, unless the application number and filing date are identified in the Power of Attorney by Applicant form. If neither form PTO/AIA/82A nor form PTO/AIA82B identifies the application to which the Power of Attorney is directed, the Power of Attorney will not be recognized in the application.

Application Number	14/069,927
Filing Date	November 1, 2013
First Named Inventor	Fabio TRENTO
Title	COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING
Art Unit	1612
Examiner Name	Walter E. Webb
Attorney Docket Number	HHC002US4

SIGNATURE of Applicant or Patent Practitioner

Signature	Clark G. Sullivan	Date (Optional)	June 12, 2018
Name	Clark G Sullivan	Registration Number	36942
Title (if Applicant is a juristic entity)			
Applicant Name (if Applicant is a juristic entity)			

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

☐ *Total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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

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

PTO/AIA/82B (07-13)
Approved for use through 11/30/2014. OMB 0651-0051
U.S. Patent and Trademark Office, U.S. DEPARTMENT OF COMMERCE
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POWER OF ATTORNEY BY APPLICANT

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

Application Number	Filing Date

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

☑ I hereby appoint the Patent Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above: 140619

OR

☐ I hereby appoint Practitioner(s) named in the attached list (form PTO/AIA/82C) as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the patent application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above (Note: Complete form PTO/AIA/82C)

Please recognize or change the correspondence address for the application identified in the attached transmittal letter or the boxes above to:

☑ The address associated with the above-mentioned Customer Number

OR

☐ The address associated with Customer Number:

OR

Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Email			

I am the Applicant (if the Applicant is a juristic entity, list the Applicant name in the box):

Helsinn Healthcare SA

☐ Inventor or Joint Inventor (title not required below)

☐ Legal Representative of a Deceased or Legally Incapacitated Inventor (title not required below)

☑ Assignee or Person to Whom the Inventor is Under an Obligation to Assign (provide signer's title if applicant is a juristic entity)

☐ Person Who Otherwise Shows Sufficient Proprietary Interest (e.g., a petition under 37 CFR 1.46(b)(2) was granted in the application or is concurrently being filed with this document) (provide signer's title if applicant is a juristic entity)

SIGNATURE of Applicant for Patent

The undersigned (whose title is supplied below) is authorized to act on behalf of the applicant (e.g., where the applicant is a juristic entity).

Signature		Date (Optional)	
Name	Matteo Missaglia		
Title	GENERAL COUNSEL & CHIEF LEGAL OFFICER		

NOTE: Signature - This form must be signed by the applicant in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. If more than one applicant, use multiple forms.

☐ Total of forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33 The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2

APPENDIX B

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AKYNZEO® safely and effectively. See full prescribing information for AKYNZEO®.

AKYNZEO® (netupitant and palonosetron) capsules, for oral use
Initial U.S. Approval: 2014

AKYNZEO® (fosnetupitant and palonosetron) for injection, for intravenous use
Initial U.S. Approval: 2018

----------RECENT MAJOR CHANGES----------

Indication and Usage (1)	04/2018
Dosage and Administration, Recommended Dosage (2.1)	04/2018
Dosage and Administration, Preparation (2.2)	04/2018
Dosage and Administration, Incompatibility (2.3)	04/2018

----------INDICATIONS AND USAGE----------

- AKYNZEO capsules is indicated in combination with dexamethasone in adults for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy.

- AKYNZEO for injection is indicated in combination with dexamethasone in adults for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy.

  Limitations of Use
  AKYNZEO for injection has not been studied for the prevention of nausea and vomiting associated with anthracycline plus cyclophosphamide chemotherapy.

- AKYNZEO is a combination of palonosetron, a serotonin-3 (5-HT_3) receptor antagonist, and netupitant or fosnetupitant, substance P/neurokinin-1 (NK-1) receptor antagonists: palonosetron prevents nausea and vomiting during the acute phase and netupitant/fosnetupitant prevents nausea and vomiting during both the acute and delayed phase after cancer chemotherapy. (1)

----------DOSAGE AND ADMINISTRATION----------

- One AKYNZEO capsule administered approximately 1 hour prior to the start of chemotherapy, with or without food. (2.1)
- One vial of AKYNZEO for injection; reconstituted in 50 ml of 5% Dextrose Injection, USP or 0.9% Sodium Chloride Injection, USP and administered as 30-minute infusion starting approximately 30 minutes prior to the start of chemotherapy. (2.1, 2.2, 2.3)

----------DOSAGE FORMS AND STRENGTHS----------

- Capsules: 300 mg netupitant/0.5 mg palonosetron
- For Injection: 235 mg fosnetupitant/0.25 mg palonosetron lyophilized powder in a single-dose vial for reconstitution (3)

----------CONTRAINDICATIONS----------

None (4)

----------WARNINGS AND PRECAUTIONS----------

- Hypersensitivity reactions, including anaphylaxis, have been reported in patients receiving palonosetron, one of the components of AKYNZEO, with or without known hypersensitivity to other 5-HT_3 receptor antagonists. (5.1)
- Serotonin syndrome has been reported with 5-HT_3 receptor antagonists alone but particularly with concomitant use of serotonergic drugs. If such symptoms occur, discontinue AKYNZEO and initiate supportive treatment. If concomitant use of AKYNZEO with other serotonergic drugs is clinically warranted, patients should be made aware of a potential increased risk for serotonin syndrome. (5.2, 7.3)

----------ADVERSE REACTIONS----------

Most common adverse reactions (≥3%) for AKYNZEO capsules are headache, asthenia, dyspepsia, fatigue, constipation and erythema (6.1)
The safety profile of AKYNZEO for injection was generally similar to that seen with AKYNZEO capsules. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact HELSINN at 1-844-357-4668 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- CYP3A4 Substrates: inhibition of CYP3A4 by netupitant can result in increased plasma concentrations of the concomitant drug for 6 days after single dosage administration of AKYNZEO; avoid concomitant CYP3A4 substrates for one week, if feasible. If not avoidable, consider dose reduction of the CYP3A4 substrate (7.1)
- CYP3A4 Inducers (e.g., rifampin): decreased plasma concentrations of netupitant; avoid use (7.2)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: May cause fetal harm (8.1).
- Hepatic Impairment: Avoid use in patients with severe hepatic impairment (8.6)
- Renal Impairment: Avoid use in patients with severe renal impairment or end-stage renal disease (8.7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 04/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Recommended Dosage
2.2 Preparation and Administration of AKYNZEO for Injection
2.3 Incompatibility of AKYNZEO for Injection
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Hypersensitivity
5.2 Serotonin Syndrome
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
7 DRUG INTERACTIONS
7.1 Effects of AKYNZEO on Other Drugs
7.2 Effects of Other Drugs on AKYNZEO
7.3 Serotonergic Drugs
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.4 Pediatric Use

8.5 Geriatric Use
8.6 Hepatic Impairment
8.7 Renal Impairment
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

- AKYNZEO capsules is indicated in combination with dexamethasone in adults for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy. AKYNZEO capsules is a combination of palonosetron and netupitant: palonosetron prevents nausea and vomiting during the acute phase and netupitant prevents nausea and vomiting during both the acute and delayed phase after cancer chemotherapy.

- AKYNZEO for injection is indicated in combination with dexamethasone in adults for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy. AKYNZEO for injection is a combination of palonosetron and fosnetupitant, a prodrug of netupitant: palonosetron prevents nausea and vomiting during the acute phase and fosnetupitant prevents nausea and vomiting during both the acute and delayed phase after cancer chemotherapy.

  Limitations of Use

  AKYNZEO for injection has not been studied for the prevention of nausea and vomiting associated with anthracycline plus cyclophosphamide chemotherapy.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosages of AKYNZEO and dexamethasone in adults for the prevention of nausea and vomiting associated with administration of emetogenic chemotherapy are shown in Table 1.

AKYNZEO capsules can be taken with or without food.

Table 1: Antiemetic Treatment Regimen

Treatment Regimen	Day 1		Days 2 to 4
Highly Emetogenic Chemotherapy, including Cisplatin-Based Chemotherapy			
AKYNZEO capsules	1 capsule of AKYNZEO	1 hour before chemotherapy	Dexamethasone 8 mg once a day
	Dexamethasone 12 mg	30 minutes before chemotherapy	
AKYNZEO for injection	1 vial of AKYNZEO	Infuse over 30 minutes starting 30 minutes before chemotherapy *[see Dosage and Administration (2.2)]*	Dexamethasone 8 mg once a day
	Dexamethasone 12 mg	30 minutes before chemotherapy	
Anthracyclines and Cyclophosphamide-Based Chemotherapy and Chemotherapy Not Considered Highly Emetogenic			
AKYNZEO capsules	1 capsule of AKYNZEO	1 hour before chemotherapy	None
	Dexamethasone 12 mg	30 minutes before chemotherapy	

2.2 Preparation and Administration of AKYNZEO for injection

Preparation

See Table 2 for preparation instructions.

AKYNZEO for injection contains no antimicrobial preservatives and is intended for single use only.

Table 2: Preparation of AKYNZEO for Injection

Step 1	Aseptically inject 20 mL 5% Dextrose Injection, USP or 0.9% Sodium Chloride Injection, USP into the vial. Ensure the solvent is added to the vial along the vial wall and not jetted in order to prevent foaming. Swirl the vial gently.
Step 2	Aseptically prepare an infusion vial or bag filled with 30 mL of 5% Dextrose Injection, USP or 0.9% Sodium Chloride Injection, USP.
Step 3	Aseptically withdraw the entire volume of reconstituted solution from the AKYNZEO vial and transfer it into the infusion vial or bag containing 30 mL of 5% Dextrose Injection, USP or 0.9% Sodium Chloride Injection, USP to yield a total volume of 50 mL.
Step 4	Gently invert the vial or bag until complete dissolution.
Step 5	Before administration, inspect the final diluted solution for particulate matter and discoloration. Discard the vial or bag if particulates and/or discoloration are observed.

Administration

Administer over 30 minutes as an intravenous infusion.

At the end of the infusion, flush the infusion line with the same carrier solution to ensure complete drug administration.

Storage

The total time from reconstitution to the start of the infusion should not exceed 3 hours. Store the reconstituted solution and the final diluted solution at room temperature.

2.3 Incompatibility of AKYNZEO for Injection

AKYNZEO for injection is incompatible with any solution containing divalent cations (e.g., calcium, magnesium), including Lactated Ringer's Injection and Hartmann's Solution.

Limited data are available on the compatibility of AKYNZEO for injection with other intravenous substances, additives or other medications, and they should not be added to the AKYNZEO solution or infused simultaneously. If the same intravenous line is used for sequential infusion of several different drugs, flush the line before and after infusion of AKYNZEO solution with 0.9% Sodium Chloride Injection, USP.

3 DOSAGE FORMS AND STRENGTHS

Capsules: 300 mg netupitant/0.5 mg palonosetron in a hard gelatin capsule with white body and caramel cap with "HE1" printed on the body.

For Injection: 235 mg fosnetupitant/0.25 mg palonosetron white to off-white lyophilized powder in single-dose vial for reconstitution.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity

Hypersensitivity reactions, including anaphylaxis, have been reported in patients treated with palonosetron, one of the components of AKYNZEO, with or without known hypersensitivity to other 5-HT_3 receptor antagonists.

5.2 Serotonin Syndrome

The development of serotonin syndrome has been reported with 5-HT_3 receptor antagonists. Most reports have been associated with concomitant use of serotonergic drugs (e.g., selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors, mirtazapine, fentanyl, lithium, tramadol, and intravenous methylene blue). Some of the reported cases were fatal. Serotonin syndrome occurring with overdose of another 5-HT_3 receptor antagonist alone has also been reported. The majority of reports of serotonin syndrome related to 5-HT_3 receptor antagonist use occurred in a post-anesthesia care unit or an infusion center.

Symptoms associated with serotonin syndrome may include the following combination of signs and symptoms: mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, and hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, and incoordination), seizures, with or without gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Patients should be monitored for the emergence of serotonin syndrome, especially with concomitant use of AKYNZEO and other serotonergic drugs. If symptoms of serotonin syndrome occur, discontinue AKYNZEO and initiate supportive treatment. Patients should be informed of the increased risk of serotonin syndrome, especially if AKYNZEO is used concomitantly with other serotonergic drugs *[see Drug Interactions (7.3)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are found elsewhere in the labeling:

- Hypersensitivity Reactions *[see Warnings and Precautions (5.1)]*
- Serotonin Syndrome *[see Warnings and Precautions (5.2)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

AKYNZEO Capsules

The overall safety of AKYNZEO capsules was evaluated in 1538 cancer patients and healthy subjects in clinical trials. The data described below reflect exposure to AKYNZEO in 1169 cancer patients, receiving at least one cycle of cancer chemotherapy in 3 active-controlled trials *[see Clinical Studies (14.1)]*, including 782 exposed to AKYNZEO for at least 4 cycles and 321 exposed for at least 6 cycles, up to a maximum of 12 cycles of chemotherapy. The median age was 55, 79% were female, 83% were White, 13% were Asian, and 4% were Hispanic. All patients received a single oral dose of AKYNZEO 1 hour prior to the start of each chemotherapy cycle. In all studies, dexamethasone was co-administered with AKYNZEO *[see Clinical Studies (14.1), Table 14 and Table 16]*.

Cisplatin Based Highly Emetogenic Chemotherapy

In a single-cycle study of patients receiving cisplatin based highly emetogenic chemotherapy, 136 patients were treated with AKYNZEO. Table 3 shows adverse reactions reported at an incidence of at least 3% and for which the AKYNZEO rate exceeded palonosetron alone.

Table 3: Adverse Reactions Occurring in ≥3% of Cancer Patients Receiving AKYNZEO Capsules and Cisplatin Based Highly Emetogenic Chemotherapy (Cycle 1)

Adverse Reactions	AKYNZEO Capsules netupitant 300 mg/ palonosetron 0.5 mg (N=136)	Palonosetron 0.5 mg (N=136)
Dyspepsia	4%	2%
Fatigue	4%	2%
Constipation	3%	1%
Erythema	3%	2%

Anthracyclines and Cyclophosphamide Based Chemotherapy

In a study of patients receiving anthracycline and cyclophosphamide based chemotherapy, 725 patients were treated with AKYNZEO capsules during Cycle 1, and 635 of these patients continued for up to 8 cycles in a multiple-cycle extension. Table 4 shows adverse reactions reported at an incidence of at least 3% and for which the AKYNZEO capsules rate exceeded palonosetron alone during Cycle 1. The adverse reaction profile in subsequent cycles was similar to that observed in Cycle 1.

Table 4: Adverse Reactions Occurring in ≥3% of Cancer Patients Receiving AKYNZEO Capsules and Anthracyclines and Cyclophosphamide Based Chemotherapy (Cycle 1)

Adverse Reactions	AKYNZEO Capsules netupitant 300 mg/palonosetron 0.5 mg (N=725)	Palonosetron 0.5 mg (N=725)
Headache	9%	7%
Asthenia	8%	7%
Fatigue	7%	5%

In addition to the adverse reactions shown above, there were reports of concomitant elevations of transaminases greater than 3 times the upper limit of normal and total bilirubin in both arms of the two trials that compared AKYNZEO capsules to oral palonosetron, and the frequency of these elevations was comparable between treatment groups. See Table 5.

Table 5: Liver Function Laboratory Abnormalities

Laboratory Changes	AKYNZEO Capsules netupitant 300 mg/palonosetron 0.5 mg (N=861)	Palonosetron 0.5 mg (N=861)
AST > 3 x ULN and/or ALT > 3 x ULN with Total Bilirubin > ULN	3 (0.3%)	5 (0.6%)
AST > 10 x ULN and/or ALT > 10 x ULN with Total Bilirubin > ULN	–	2 (0.2%)
AST > 3 x ULN and/or ALT > 3 x ULN with Total Bilirubin ≥ 2 x ULN	1 (0.1%)	1 (0.1%)

ULN = upper limit of normal

In a multi-cycle safety study of 412 patients, the safety profile of AKYNZEO capsules (n = 308) was comparable to aprepitant and palonosetron (n = 104) in patients undergoing initial and repeat cycles (median 5 cycles, range of 1-14 cycles) of chemotherapy, including carboplatin, cisplatin, oxaliplatin, and doxorubicin regimens. There were no reports of concomitant elevations of transaminases greater than 3 times the upper limit of normal and total bilirubin in this study in either arm.

In a randomized, clinical non-inferiority study, that compared oral palonosetron 0.5 mg to intravenous palonosetron 0.25 mg in cancer patients scheduled to receive highly emetogenic cisplatin (greater than or equal to 70 mg/m^2) based chemotherapy, there were two patients (0.5%; 2/369) in the intravenous palonosetron arm who had concomitant elevations of transaminases and total bilirubin. Neither experienced transaminase elevations greater than 10 times the upper limit of normal.

AKYNZEO for Injection

The safety of AKYNZEO for injection was evaluated in 203 patients in an active-controlled multi-cycle (median 4 cycles, range of 1-4 cycles) safety clinical study in patients receiving HEC regimens, not including anthracycline plus cyclophosphamide, (e.g., cisplatin, cyclophosphamide, carmustine, dacarbazine and mechloretamine) compared to 201 patients receiving AKYNZEO capsules (NCT02517021). The median age was 60 years, 46% were female, 99.5 % were White, 0.3% were Asian, and 0.3% were Hispanic. All patients received a single dose of AKYNZEO for injection 30 minutes prior to the start of each chemotherapy cycle; dexamethasone was co-administered with AKYNZEO. The safety profile of AKYNZEO for injection was generally similar to that seen with AKYNZEO capsules.

7 DRUG INTERACTIONS

7.1 Effects of AKYNZEO on Other Drugs

Interaction with CYP3A4 Substrates

Netupitant is a moderate inhibitor of CYP3A4.

AKYNZEO should be used with caution in patients receiving concomitant medications that are primarily metabolized through CYP3A4. A single oral dose of netupitant 300 mg significantly inhibits CYP3A4 for 6 days. Avoid concomitant use of drugs that are CYP3A4 substrates for one week, if feasible. If not avoidable, consider dose reduction of CYP3A4 substrates.

Dexamethasone

A single oral dose of netupitant 300 mg or a single fosnetupitant infusion of 235 mg increased the systemic exposure of concomitant dexamethasone more than 2-fold on Days 2 and 4. Administer a reduced dose of dexamethasone with AKYNZEO *[see Dosage and Administration (2.1), Clinical Pharmacology (12.3)]*.

Midazolam

When administered with netupitant, the systemic exposure to midazolam was significantly increased. Consider the potential effects of increased plasma concentrations of midazolam or

other benzodiazepines metabolized via CYP3A4 (alprazolam, triazolam) when administering these drugs with AKYNZEO *[see Clinical Pharmacology (12.3)]*.

Chemotherapeutic Agents

The systemic exposure of chemotherapy agents metabolized by CYP3A4 can increase when administered with AKYNZEO. Chemotherapy agents that are known to be metabolized by CYP3A4 include docetaxel, paclitaxel, etoposide, irinotecan, cyclophosphamide, ifosfamide, imatinib, vinorelbine, vinblastine, and vincristine *[see Clinical Pharmacology (12.3)]*. Caution and monitoring for chemotherapeutic related adverse reactions are advised in patients receiving chemotherapy agents metabolized primarily by CYP3A4.

Oral Contraceptives

There is no clinically significant effect of AKYNZEO on the efficacy of oral contraceptives containing levonorgestrel and ethinyl estradiol *[see Clinical Pharmacology (12.3)]*.

Warfarin

Although it was predicted that co-administration of intravenous AKYNZEO with warfarin would not substantially increase the systemic exposure to S-warfarin (CYP2C9 substrate), the active enantiomer, the effects of AKYNZEO for injection and AKYNZEO capsules on INR and prothrombin time have not been studied. Monitor INR and adjust the dosage of warfarin, as needed with concomitant use of AKYNZEO, to maintain the target INR range.

7.2 Effects of Other Drugs on AKYNZEO

Netupitant is mainly metabolized by CYP3A4.

Palonosetron is mainly metabolized by CYP2D6 and to a lesser extent by CYP3A4 and CYP1A2.

CYP3A4 Inducers

Avoid concomitant use of AKYNZEO in patients who are chronically using a strong CYP3A4 inducer such as rifampin. A strong CYP3A inducer can decrease the efficacy of AKYNZEO by substantially reducing plasma concentrations of the netupitant component *[see Clinical Pharmacology (12.3)]*.

CYP3A4 Inhibitors

Concomitant use of AKYNZEO with a strong CYP3A4 inhibitor (e.g., ketoconazole) can increase the systemic exposure to the netupitant component of AKYNZEO. However, no dosage adjustment is necessary for single dose administration of AKYNZEO *[see Clinical Pharmacology (12.3)]*.

7.3 Serotonergic Drugs

Serotonin syndrome (including altered mental status, autonomic instability, and neuromuscular symptoms) has been described following the concomitant use of 5-HT_3 receptor antagonists and other serotonergic drugs, including selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs). If symptoms occur, discontinue AKYNZEO and initiate supportive treatment *[see Warnings and Precautions (5.2)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Limited available data with AKYNZEO use in pregnant women are insufficient to inform a drug-associated risk of adverse developmental outcomes. In animal reproduction studies with netupitant, no effects on embryo-fetal development were observed following daily oral administration in pregnant rats during the period of organogenesis at doses up to 3.7 times the human AUC (area under the plasma concentration-time curve) at the recommended single dose to be given with each cycle of chemotherapy. However, a dose-dependent increase in adverse effects on embryo-fetal development was observed following daily oral administration of netupitant in pregnant rabbits during the period of organogenesis with doses at least 0.2 times the human AUC at the recommended single dose to be given with each cycle of chemotherapy. Daily oral administration of netupitant in rats up to 3.7 times the human AUC at the recommended dose during organogenesis through lactation produced no adverse effects in the offspring *(see Data).*

In animal reproduction studies with fosnetupitant, delayed ossification of pubis occurred after intravenous administration in rats during the period of organogenesis at a dose 3 times the human AUC for netupitant at the recommended single dose to be given with each cycle of chemotherapy. In pregnant rabbits, an increase in resorptions was observed with daily intravenous administration of fosnetupitant during the period of organogenesis at doses up to 9 times the human AUC for fosnetupitant and 0.4 times the human AUC for netupitant at the recommended single dose to be given with each cycle of chemotherapy. Daily intravenous administration of fosnetupitant (3 times the human AUC for netupitant at the recommended single dose to be given with each cycle of chemotherapy) in rats during organogenesis through lactation produced lower bodyweight in offspring at birth through maturation, and delayed physical development *(see Data).*

In animal reproduction studies with palonosetron, no effects on embryo-fetal development were observed following oral administration during the period of organogenesis at doses up to 921 and 1841 times the recommended oral dose in rats and rabbits, respectively *(see Data).*

Based on animal data from netupitant studies, advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated populations are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

Netupitant

Daily oral administration of up to 30 mg/kg netupitant in rats (3.7 times the human AUC at the recommended single dose to be given with each cycle of chemotherapy) during the period of

organogenesis produced no effects on embryo-fetal development. However, an increased incidence of external and skeletal abnormalities in rabbit fetuses was observed following daily oral administration of netupitant in rabbits at 10 mg/kg/day and higher (0.2 times the human AUC at the recommended single dose to be given with each cycle of chemotherapy) during the period of organogenesis. These abnormalities included positional abnormalities in the limbs and paws, and fused sternebrae. Reduction in fetal rabbit weight occurred at 30 mg/kg/day. Maternal toxicity in rabbits (i.e., loss of bodyweight during the treatment period) was also observed at 30 mg/kg/day. Daily oral administration of up to 30 mg/kg netupitant (3.7 times the human AUC at the recommended dose) in rats during organogenesis through lactation produced no adverse effects in the offspring.

Fosnetupitant

Daily intravenous administration of 39 mg/kg/day fosnetupitant in rats (3 times the human AUC for netupitant at the recommended single dose to be given with each cycle of chemotherapy) during the period of organogenesis produced delayed ossification of pubis. No effects on embryo-fetal development were observed with daily administration of up to 13 mg/kg fosnetupitant in rats (2 times the human AUC for netupitant at the recommended single dose to be given with each cycle of chemotherapy). Due to the limited systemic exposure to fosnetupitant in pregnant rats, it is not possible to provide an AUC-based comparison of fosnetupitant exposure in rats and humans. An increase in resorptions was observed with daily intravenous administration of fosnetupitant at 6 mg/kg/day and higher in rabbits (9 times the human AUC for fosnetupitant and 0.4 times the human AUC for netupitant at the recommended single dose to be given with each cycle of chemotherapy) during the period of organogenesis. No effects were observed in rabbits at 3 mg/kg/day (5.4 times the human AUC for fosnetupitant and 0.4 times the human AUC for netupitant at the recommended single dose to be given with each cycle of chemotherapy). Daily intravenous administration of 39 mg/kg fosnetupitant in rats (3 times the AUC for netupitant at the recommended single dose to be given with each cycle of chemotherapy) during organogenesis through lactation produced lower bodyweight in offspring at birth through maturation, and delayed physical development (pinna detachment, eye opening, and preputial separation). These effects were associated with maternal toxicity (reduced weight gain and food consumption). No effects occurred in offspring or dams at 13 mg/kg/day (2 times the human AUC for netupitant at the recommended single dose to be given with each cycle of chemotherapy).

Palonosetron

In animal reproduction studies with palonosetron, no effects on embryo-fetal development were observed in pregnant rats given oral doses up to 60 mg/kg/day (921 times the recommended oral dose based on body surface area) or pregnant rabbits given oral doses up to 60 mg/kg/day (1841 times the recommended oral dose based on body surface area) during the period of organogenesis.

8.2 Lactation

Risk Summary

There are no data on the presence of netupitant (or fosnetupitant) or palonosetron in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for

AKYNZEO and any potential adverse effect on the breastfed child from AKYNZEO or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of AKYNZEO in patients below the age of 18 years have not been established.

8.5 Geriatric Use

Of the 1169 adult cancer patients treated with AKYNZEO capsules in clinical studies, 18% were aged 65 and over, while 2% were aged 75 years and over. The nature and frequency of adverse reactions were similar in elderly and younger patients. Exploratory analyses of the impact of age on efficacy were performed in the two trials that compared AKYNZEO to palonosetron *[see Clinical Studies (14)]*. In Study 1 in patients treated with cisplatin chemotherapy, among the patients less than age 65 years, 115 were treated with AKYNZEO and 116 were treated with palonosetron alone. Among the patients 65 years or older, 20 were treated with AKYNZEO and 20 were treated with palonosetron alone. The difference in Complete Response (CR) rates between AKYNZEO and palonosetron alone was similar between the two age groups in both the acute and delayed phases. In Study 2 in patients treated with anthracyclines plus cyclophosphamide chemotherapy, among the patients less than age 65 years, 608 were treated with AKYNZEO and 602 were treated with palonosetron alone. Among the patients 65 years or older, 116 were treated with AKYNZEO and 123 were treated with palonosetron alone. The difference in CR rates between AKYNZEO and palonosetron alone (4% in <65 years and 2% in ≥65 years) was similar between the two age groups in the acute phase. In the delayed phase, the difference in CR rates between AKYNZEO and palonosetron alone (9% in <65 years and 1% in ≥ 65 years) was numerically higher in patients <65 years. This difference between age groups in the delayed phase of Study 2 may be explained, in part, by higher CR in the delayed phase associated with palonosetron alone in the older age group (81%) relative to the younger patients treated with palonosetron alone (67%).

Of the 239 adult cancer patients treated with AKYNZEO for injection in clinical studies, 36% were aged 65 and over, while 4% were aged 75 years and over. The nature and frequency of adverse reactions were similar in elderly and younger patients.

In general, use caution when dosing elderly patients as they have a greater frequency of decreased hepatic, renal or cardiac function and concomitant disease or other drug therapy.

8.6 Hepatic Impairment

No dosage adjustment for AKYNZEO is necessary for patients with mild to moderate hepatic impairment (Child-Pugh score 5 to 8). Limited data are available with AKYNZEO in patients with severe hepatic impairment (Child-Pugh score greater than 9). Avoid use of AKYNZEO in patients with severe hepatic impairment *[see Overdosage (10), Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

No dosage adjustment for AKYNZEO is necessary in patients with mild to moderate renal impairment (creatinine clearance of 30 to 60 mL/min). The pharmacokinetics and safety of netupitant have not been studied in patients with severe renal impairment. Severe renal

impairment (creatinine clearance < 30 mL/min) did not substantially affect pharmacokinetics of palonosetron. The pharmacokinetics for netupitant and palonosetron were not studied in patients with end-stage renal disease requiring hemodialysis. Avoid use of AKYNZEO in patients with severe renal impairment or end-stage renal disease *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

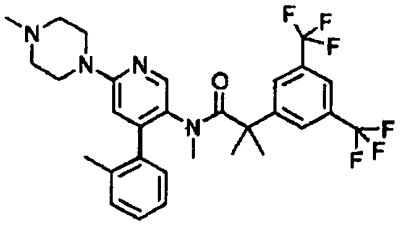
In the event of overdose, AKYNZEO should be discontinued and general supportive treatment and monitoring should be provided. Because of the antiemetic activity of AKYNZEO, drug-induced emesis may not be effective. Dialysis studies have not been performed; due to the large volume of distribution, dialysis is unlikely to be an effective treatment for AKYNZEO overdose.

A total of 33 adult cancer patients were administered oral palonosetron at a dose of 90 mcg/kg (approximately 12 times the recommended dose in AKYNZEO capsules), as part of a dose ranging study and had a similar incidence of adverse reactions compared to lower doses. A single dose of 600 mg (2 times the recommended dose in AKYNZEO capsules) of oral netupitant was administered to 49 healthy subjects and a similar incidence of adverse reactions was observed when compared to lower doses of netupitant in cancer patients and healthy subjects.

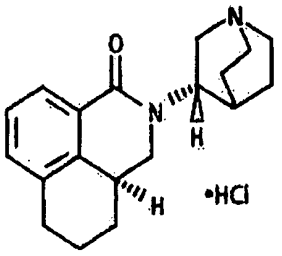
11 DESCRIPTION

AKYNZEO (300 mg netupitant/0.5 mg palonosetron) capsules are an oral combination product of netupitant, a substance P/neurokinin 1 (NK-1) receptor antagonist, and palonosetron hydrochloride, a serotonin-3 (5-HT_3) receptor antagonist. Both netupitant and palonosetron hydrochloride are anti-nausea and anti-emetic agents.

Netupitant is chemically described: 2-[3,5-bis(trifluoromethyl)phenyl]-N, 2 dimethyl-N-[4-(2-methylphenyl)-6-(4-methylpiperazin-1-yl)pyridin-3-yl] propanamide. The empirical formula is $C_{30}H_{32}F_6N_4O$, with a molecular weight of 578.61. Netupitant exists as a single isomer and has the following structural formula:



Palonosetron hydrochloride is chemically described: (3aS)-2-[(S)-1-Azabicyclo [2.2.2]oct-3-yl]-2,3,3a,4,5,6-hexahydro-1-oxo-1H-benz[de]isoquinoline hydrochloride. The empirical formula is $C_{19}H_{24}N_2O.HCl$, with a molecular weight of 332.87. Palonosetron hydrochloride exists as a single isomer and has the following structural formula:



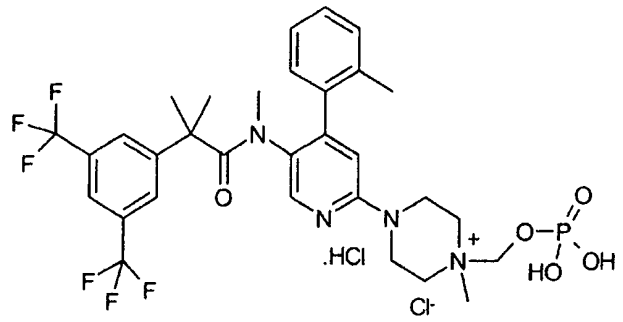
Netupitant is white to off-white crystalline powder. It is freely soluble in toluene and acetone, soluble in isopropanol and ethanol, and very slightly soluble in water.

Palonosetron hydrochloride is a white to off-white crystalline powder. It is freely soluble in water, soluble in propylene glycol, and slightly soluble in ethanol and 2-propanol.

Each AKYNZEO capsule is composed of one white-caramel hard gelatin capsule which contains three tablets each containing 100 mg netupitant and one gelatin capsule containing 0.5 mg palonosetron (equivalent to 0.56 mg palonosetron hydrochloride). The inactive ingredients are butylated hydroxyanisole (BHA), croscarmellose sodium, gelatin, glycerin, magnesium stearate, microcrystalline cellulose, mono- and di-glycerides of capryl/capric acid, polyglyceryl dioleate, povidone K-30, purified water, red iron oxide, silicon dioxide, sodium stearyl fumarate, sorbitol, sucrose fatty acid esters, titanium dioxide and yellow iron oxide. It may contain traces of medium-chain triglycerides, lecithin, and denatured ethanol.

AKYNZEO (235 mg fosnetupitant/0.25 mg palonosetron) for injection is a combination product of fosnetupitant, a prodrug of netupitant, which is a substance P/neurokinin 1 (NK-1) receptor antagonist, and palonosetron hydrochloride, a serotonin-3 (5-HT_3) receptor antagonist.

Fosnetupitant chloride hydrochloride is chemically described as 2-(3,5-bis-trifluoromethylphenyl)-N-methyl-N-[6-(4-methyl-4-O-methylene-phosphatepiperazinium-1-yl)-4-o-tolyl-pyridin-3-yl]-isobutyramide chloride hydrochloride. The empirical formula is $C_{31}H_{36}F_6N_4O_5P$•Cl•HCl, with a molecular weight of 761.53. Fosnetupitant chloride hydrochloride exists as a single isomer and has the following structural formula:



Fosnetupitant chloride hydrochloride is white to off-white to yellowish solid or powder. Its solubility is pH dependent: at acidic pH (pH 2), its solubility is 1.4 mg/mL; at basic pH (pH 10), its solubility is 11.5 mg/mL.

Palonosetron hydrochloride is described above in this section.

AKYNZEO for injection is available for intravenous infusion, and is supplied as a sterile lyophilized powder in a single-dose vial. Each vial contains 235 mg of fosnetupitant (equivalent to 260 mg fosnetupitant chloride hydrochloride) and 0.25 mg of palonosetron (equivalent to 0.28 mg of palonosetron hydrochloride). The inactive ingredients are edetate disodium (6.4 mg), mannitol (760 mg), sodium hydroxide and/or hydrochloric acid (for pH adjustment).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Netupitant is a selective antagonist of human substance P/neurokinin 1 (NK-1) receptors.

Palonosetron is a 5-HT_3 receptor antagonist with a strong binding affinity for this receptor and little or no affinity for other receptors. Cancer chemotherapy may be associated with a high incidence of nausea and vomiting, particularly when certain agents, such as cisplatin, are used. 5-HT_3 receptors are located on the nerve terminals of the vagus in the periphery and centrally in the chemoreceptor trigger zone of the area postrema. Chemotherapeutic agents produce nausea and vomiting by stimulating the release of serotonin from the enterochromaffin cells of the small intestine. Serotonin then activates 5-HT_3 receptors located on vagal afferents to initiate the vomiting reflex. The development of acute emesis is known to depend on serotonin and its 5-HT_3 receptors have been demonstrated to selectively stimulate the emetic response.

Delayed emesis has been largely associated with the activation of tachykinin family neurokinin 1 (NK-1) receptors (broadly distributed in the central and peripheral nervous systems) by substance P. As shown in *in vitro* and *in vivo* studies, netupitant inhibits substance P mediated responses.

12.2 Pharmacodynamics

NK-1 Receptor Occupancy

The receptor occupancy of netupitant was measured in a human Positron Emission Tomography (PET) study. Netupitant was shown to cross the blood brain barrier with a NK-1 receptor occupancy of 92.5%, 86.5%, 85.0%, 78.0%, and 76.0% in striatum at 6, 24, 48, 72, and 96 hours, respectively, after oral administration of 300 mg netupitant.

Cardiac Electrophysiology

An AKYNZEO oral dose of 600 mg netupitant (2 times the recommended dose) and 1.5 mg palonosetron (3 times the recommended dose) did not prolong the QT interval to any clinically relevant extent.

The recommended dose of AKYNZEO for injection (235 mg fosnetupitant and 0.25 mg palonosetron) did not prolong the QT interval to any clinically relevant extent.

12.3 Pharmacokinetics

Netupitant and Palonosetron

Absorption

Upon single oral administration of AKYNZEO capsules to healthy subjects and patients, netupitant and palonosetron were measurable within 1 hour after administration and reached the maximum concentration (C_{max}) in approximately 4 to 5 hours (Table 6).

Table 6: Systemic Exposure (AUCinf and Cmax) of Netupitant and Palonosetron After a Single Oral Dose of AKYNZEO in Healthy Subjects and Cancer Patients

Parameter	Population	Mean (CV%[2])	
		Netupitant	Palonosetron
AUC_{inf} (ng·h/mL)	Healthy Subjects	14,402 (51)	56.7 (33)
	Patients	17,365 (39)	58.3 (50)
C_{max} (ng/mL)	Healthy Subjects	434 (56)	1.53 (25)
	Patients	496 (49)	0.95 (35)
t_{max} (h)[1]	Healthy Subjects	5 (2 to 12)	5 (1 to 12)
	Patients	4 (2 to 8)	5 (1 to 12)

[1] median (min-max); [2]CV: coefficient of variation; AUC_{inf}: area under the plasma concentration-time curve from time 0 to infinity; t_{max}: time to maximum concentration.

Following oral administration, the absolute bioavailability of palonosetron was approximately 97%.

When AKYNZEO capsules were administered under fed conditions, the systemic exposure to netupitant and palonosetron was similar to the exposure under fasting conditions.

In cancer patients who received a single dose of AKYNZEO capsules 1 hour prior to chemotherapy (docetaxel, etoposide, or cyclophosphamide), the C_{max} and the area under the concentration-time curve from time zero to infinity (AUC_{inf}) of netupitant and its metabolites were similar to those in healthy subjects. The mean C_{max} and AUC_{inf} of palonosetron in cancer patients were similar to those in healthy subjects.

No changes in pharmacokinetics of netupitant and palonosetron were observed when 450 mg oral netupitant and 0.75 mg oral palonosetron were given alone or co-administered (1.5 times the recommended dose of AKYNZEO capsules).

Dose Proportionality

Netupitant:

There was a greater than dose-proportional increase in the systemic exposure (108-fold AUC_{inf} increase for a 30-fold dose increase) when the oral netupitant dose was increased from 10 mg (approximately 3% the recommended dose in AKYNZEO capsules) to 300 mg of netupitant and a dose-proportional increase in the systemic exposure when the netupitant dose was increased from 300 mg to 450 mg of netupitant (1.5 times the recommended dose in AKYNZEO capsules).

Palonosetron:

After single oral doses of palonosetron ranging from 0.25 to 6.8 mg (0.5 to 13.6 times the recommended dose in AKYNZEO capsules) using a buffered solution, the mean C_{max} and AUC_{inf} were dose proportional in healthy subjects.

Following single intravenous doses of AKYNZEO for injection in patients or fosnetupitant in healthy subjects, C_{max} of netupitant and palonosetron were achieved at the end of the 30-minute infusion (**Table 7**).

Table 7: Systemic Exposure (AUC0-120 and Cmax) of Netupitant and Palonosetron After a Single Intravenous Dose of AKYNZEO for Injection in Cancer Patients or a Single Intravenous Dose of Fosnetupitant in Healthy Subjects

Parameter	Population	Mean (CV%[2])	
		Netupitant	Palonosetron
AUC_{0-120} (ng·h/mL)	Healthy Subjects	12,012 (19)	--
	Patients	8,922 (22)	28 (28)
C_{max} (ng/mL)	Healthy Subjects	841 (21)	--
	Patients	590 (28)	0.8 (35)
t_{max} (h)[1]	Healthy Subjects	0.5 (0.5 to 0.4)	--
	Patients	0.6 (0.5 to 4)	0.6 (0.5 to 6)

[1] median (min-max); [2]CV: coefficient of variation; AUC_{0-120}: AUC from time 0 to 120 hours from start of infusion

Distribution

After single oral administration of AKYNZEO capsules, netupitant and palonosetron were widely distributed throughout the body (Table 8).

Table 8: Volume of Distribution (Vz/F) in Healthy Subjects and Cancer Patients After a Single Oral Dose of AKYNZEO and In Vitro Protein Binding

Parameter	Population	Mean (CV%[c])	
		Netupitant	Palonosetron
Vz/F (L)	Healthy Subjects	3314 (53)	586 (33)
	Patients	1982 (46)	663 (24)
Plasma Protein Binding	*In vitro* studies	Netupitant: > 99.5%[a] Major Metabolites: > 97%[b]	62%

[a] Concentration range: 10 to 1300 ng/mL; [b] Concentration range: 100 to 200 ng/mL; [c]CV: coefficient of variation

After administration of single dose of AKYNZEO for injection in patients, the mean ± SD of volume of distribution (Vz) of netupitant and palonosetron were 2627 ± 990 L and 594 ± 239 L, respectively, consistent with previous estimates after single oral administration of AKYNZEO capsules in healthy subjects and cancer patients (Table 8).

Elimination – Netupitant

After a single dose of AKYNZEO capsules, netupitant is eliminated from the body in a multi-exponential fashion and the mean ± SD of apparent elimination half-life was of 96 ± 59 hours in healthy subjects and 80 ± 29 hours in cancer patients. The mean ± SD of estimated systemic clearance (CL/F) was 26.3 ± 12.5 L/h in healthy subjects and 20.3 ± 9.2 L/h in patients.

In patients, following intravenous infusion of AKYNZEO for injection, the mean ± SD total body clearance (CL) and terminal half-life ($t_{1/2}$) of netupitant were 14.1 ± 5.3 L/h and 144 ± 73 hours, respectively.

Metabolism

Once absorbed, netupitant is extensively metabolized to form three major metabolites: desmethyl derivative, M1; N-oxide derivative, M2; and OH-methyl derivative, M3. Metabolism is mediated primarily by CYP3A4 and to a lesser extent by CYP2C9 and CYP2D6. Metabolites M1, M2 and M3 were shown to bind to the substance P/neurokinin 1 (NK-1) receptor.

The mean AUC_{inf} for metabolites M1, M2 and M3 was 29%, 14% and 33% of netupitant, respectively. The median t_{max} for metabolite M2 was 5 hours and was about 17 to 32 hours for metabolites M1 and M3, respectively.

Excretion

After a single oral administration of [^{14}C]-netupitant, approximately half the administered radioactivity was recovered from urine and feces within 120 hours of dosing. The total of 3.95% and 70.7% of the radioactive dose was recovered in the urine and feces collected over 336 hours, respectively, and the mean fraction of an oral dose of netupitant excreted unchanged in urine is less than 1% suggesting renal clearance is not a significant elimination route for the netupitant-related entities. About 86.5% and 4.7% of administered radioactivity was estimated to be excreted via the feces and urine within 30 days post-dose.

Elimination - Palonosetron

Following oral administration of AKYNZEO capsules in healthy subjects and cancer patients, the mean (± SD) of half-life of palonosetron was 44 ± 15 hours and 50 ± 16 hours, respectively, whereas the mean ± SD of total body clearance (CL/F) was 9.6 ± 2.7 L/h and 10.0 ± 3.4 L/h, respectively.

After a single intravenous palonosetron dose of 10 mcg/kg (approximately 3 times the recommended dose in AKYNZEO for injection), the mean ± SD of total body clearance (CL) of palonosetron in healthy subjects was 12.1 ± 3.7 L/h, and renal clearance (CL_R) was 5.1 ± 2.1 L/h.

In patients, following intravenous infusion of AKYNZEO for injection, the mean ± SD total body clearance (CL) and terminal half-life ($t_{1/2}$) of palonosetron were 7.6 ± 2.6 L/h and 58 ± 27 h, respectively.

Metabolism

Palonosetron is eliminated by multiple routes with approximately 50% metabolized to form two primary metabolites: N-oxide-palonosetron and 6-S-hydroxy-palonosetron. These metabolites each have less than 1% of the 5-HT_3 receptor antagonist activity of palonosetron. *In vitro* metabolism studies have suggested that CYP2D6 and to a lesser extent CYP3A4 and CYP1A2 are involved in the metabolism of palonosetron. However, clinical pharmacokinetic parameters such as C_{max}, AUC_{inf}, CL, CL_R, V_z and $t_{1/2}$ are not significantly different between poor and extensive metabolizers of CYP2D6 substrates.

Excretion

Following administration of a single oral 0.75 mg dose of [^{14}C]-palonosetron (1.5 times the recommended dose in AZKYNZEO capsules) to six healthy subjects, 85% to 93% of the total radioactivity was excreted in urine, and 5% to 8% was eliminated in feces. The amount of unchanged palonosetron excreted in the urine represented approximately 40% of the administered dose.

Fosnetupitant

Absorption

Following single intravenous doses of AKYNZEO for injection in patients (235 mg fosnetupitant and 0.25 mg palonosetron infused in 30 minutes) or fosnetupitant in healthy subjects (235 mg fosnetupitant infused in 30 minutes), maximum concentrations of fosnetupitant were achieved at the end of the 30-minute infusion (Table 9).

Table 9: Systemic Exposure of Fosnetupitant After a Single Intravenous Dose of Fosnetupitant in Healthy Subjects or AKYNZEO for Injection in Cancer Patients

Parameter	Population	Mean (CV%[2])
C_{max} (ng/mL)	Healthy Subjects	6431 (14)
	Patients	3478 (45)
t_{max}[1] (h)	Healthy Subjects	0.5 (0.25 to 0.5)
	Patients	0.5 (0.5 to 0.6)
AUC_{inf} (ng·h/mL)	Healthy Subjects	2938 (12)
	Patients	1401 (46)

[1] median (min-max); [2]CV: coefficient of variation; AUC_{inf}: AUC from time 0 to infinity

In cross-study comparisons, the mean C_{max} and AUC_{inf} of fosnetupitant were lower in patients than in healthy subjects. Similarly, AUC_{0-120} and C_{max} of netupitant in patients were 26% and 30% lower than in healthy subjects, respectively (Table 7). The differences in systemic exposures to netupitant are clinically insignificant.

In healthy subjects, there was a dose-proportional increase in the systemic exposure when the dose of fosnetupitant was increased from 17.6 mg (7.5% of recommended dose in AKYNZEO for injection) to 353 mg (150% of recommended dose in AKYNZEO for injection).

Distribution

The mean ± SD volume of distribution (V_z) of fosnetupitant in healthy subjects and in patients was 124 ± 76 L and 296 ±535 L, respectively. The human plasma protein binding of fosnetupitant was 92% at 1 micromolar and 95% at 10 micromolar.

Elimination

After intravenous administration of AKYNZEO for injection, fosnetupitant plasma concentrations declined in a biexponential manner. Thirty minutes after the end of the infusion, the mean plasma concentration of fosnetupitant was less than 1% of C_{max}.

The mean ± SD of terminal elimination half-life and systemic plasma clearance (CL) of fosnetupitant were respectively 0.75 ± 0.40 hours and 249 ± 270 L/h in cancer patients after a single IV dose of AKYNZEO. They were 0.96 ± 0.55 hours (mean ± SD) and 90 ± 13 L/h in healthy subjects after a single intravenous dose of fosnetupitant.

Metabolism

Fosnetupitant is converted *in vivo* to netupitant by metabolic hydrolysis. In patients receiving AKYNZEO intravenously, netupitant exposure was 17-fold fosnetupitant exposure, as determined by their AUC_{inf} ratio. Netupitant metabolites M1, M2 and M3 were generated from the released netupitant. In patients, metabolite M1, M2 and M3 exposures were 32%, 21% and 28% of netupitant exposure. The median t_{max} for M1, M2, and M3 were 12, 2 and 12 hours, respectively.

Specific Populations

Geriatric Patients

In cancer patients receiving AKYNZEO capsules, population pharmacokinetic analysis indicated that age (within the range of 29 to 75 years) did not influence the pharmacokinetics of netupitant or palonosetron. In healthy elderly subjects (greater than 65 years of age) the mean AUC_{inf} and C_{max} was 25% and 36% higher, respectively, for netupitant, and 37% and 10% higher, respectively, for palonosetron compared to those in healthy younger adults (22 to 45 years of age). The increase in the systemic exposure to netupitant in the elderly subjects is not considered to be clinically significant.

Male and Female Patients

In a pooled analysis of data following AKYNZEO capsules, the C_{max} for netupitant was 35% higher in females than in males while the AUC_{inf} was similar between males and females. In female subjects, the mean AUC_{inf} for palonosetron was 35% higher and the mean C_{max} was 26% higher than in male subjects. Sex did not affect the pharmacokinetics of fosnetupitant, netupitant, netupitant metabolites and palonosetron after a single intravenous dose of AKYNZEO in patients. In healthy subjects, no effect of sex was observed on the pharmacokinetics of fosnetupitant, netupitant and its metabolites after a single intravenous dose of fosnetupitant alone. The mean ± SD of netupitant AUC_{inf} and C_{max} in patients were 15672 ± 5496 ng·h/mL and 567 ± 174 ng/mL, respectively in males and 15518 ± 4814 ng·h/mL and 609 ± 161 ng/mL, respectively in females.

Patients with Renal Impairment

Population pharmacokinetic analysis showed that mild and moderate renal impairment (creatinine clearance 30 to 60 mL/min) did not significantly affect the pharmacokinetics of netupitant in cancer patients. Netupitant has not been studied in patients with severe renal impairment (creatinine clearance less than 30 mL/min).

Mild to moderate renal impairment does not significantly affect palonosetron pharmacokinetic parameters. In a study with intravenous palonosetron, total systemic exposure to palonosetron increased by approximately 28% in patients with severe renal impairment relative to healthy subjects.

The pharmacokinetics of palonosetron and netupitant have not been studied in subjects with end-stage renal disease (creatinine clearance < 15 mL/min not on dialysis) *[see Use in Specific Populations (8.7)]*.

Patients with Hepatic Impairment

The effects of hepatic impairment on the pharmacokinetics of netupitant and palonosetron were studied following administration of a single oral dose of AKYNZEO to patients with mild (Child-Pugh score 5 to 6), moderate (Child-Pugh score 7 to 9), or severe (Child-Pugh score >9) hepatic impairment.

In patients with mild or moderate hepatic impairment, the mean AUC_{inf} of netupitant was 67% and 86% higher, respectively, than in healthy subjects and the mean C_{max} for netupitant was about 40% and 41% higher, respectively, than in healthy subjects.

In patients with mild or moderate hepatic impairment, the mean AUC_{inf} of palonosetron was 33% and 62% higher, respectively, than in healthy subjects and the mean C_{max} for palonosetron was about 14% higher and unchanged, respectively, than in healthy subjects.

The pharmacokinetics of netupitant and palonosetron were available from only two patients with severe hepatic impairment. As such the data are too limited to draw a conclusion *[see Use in Specific Populations (8.6)]*.

Drug Interaction Studies

Effect of Netupitant/Fosnetupitant and/or Palonosetron on Other Drugs

CYP3A4

In vitro studies have shown that netupitant and its metabolite M1 are inhibitors of CYP3A4. An *in vivo* study has confirmed that netupitant is a moderate inhibitor of CYP3A4.

Dexamethasone

In healthy subjects, the oral administration of a single AKYNZEO capsule with the CYP3A4 substrate dexamethasone (12 mg on day 1 followed by once-a-day administrations of 8 mg on days 2, 3, 4, 6, 8 and 10), increased the plasma concentrations of dexamethasone for 6 days (Table 10).

Table 10: Effect of a Single Dose of Oral AKYNZEO (Day 1) on the Systemic Exposure of a Co-administered CYP3A4 Substrate (Dexamethasone) in Healthy Subjects

% Change for Dexamethasone							
Day 1		Day 4		Day 6		Day 8	
C_{max}	AUC_{0-t}	C_{max}	AUC_{0-t}	C_{max}	AUC_{0-t}	C_{max}	AUC_{0-t}
2%↓	58%↑	54%↑	139%↑	29%↑	49%↑	7%↑	20%↑

*the interacting drug (dexamethasone 12 mg) was administered on day 1 with AKYNZEO and alone (8 mg) on days 2, 3, 4, 6, 8 and 10; AUC_{0-t}: AUC from time zero to time t of last measurable concentration after dexamethasone administration on Days 1, 4, 6 and 8

↑ = Increased; ↓ = Decreased

In healthy subjects, co-administration of a single intravenous fosnetupitant dose (235 mg) with a 20 mg oral dexamethasone on day 1 followed by twice-a-day administrations of 8 mg dexamethasone on days 2, 3, and 4, increased dexamethasone exposure 2.4-fold on day 4 (Table 11).

Table 11: Effect of a Single 235 mg Dose of Intravenous Fosnetupitant (Day 1) on the Systemic Exposure of a Co-administered CYP3A4 Substrate (Dexamethasone) in Healthy Subjects

% Change for Dexamethasone			
Day 1		Day 4	
C_{max}	AUC_{0-24}	C_{max}	AUC_{84-108}
3%↓	50%↑	70%↑	142%↑

*the interacting drug (dexamethasone 20 mg) was administered on day 1 with AKYNZEO and alone (8 mg bid) on Days 2,3,4; AUC_{0-24}: AUC from time 0 to 24h after dexamethasone administration on Day 1; AUC_{84-108}: AUC from time 84h to 108h after dexamethasone administration on Day 4
↑ = Increased; ↓ = Decreased

Considering the limited fosnetupitant exposure in human plasma and its conversion to netupitant within 30 minutes after completion of infusion, the effects are ascribed to netupitant *[see Drug Interactions (7.1)]*.

Midazolam

When co-administered with netupitant 300 mg the mean C_{max} and AUC_{inf} of midazolam after single dose oral administration of 7.5 mg midazolam was 36% and 126% higher, respectively *[see Drug Interactions (7.1)]*.

Chemotherapeutic Agents (docetaxel, etoposide, cyclophosphamide)

Systemic exposure to intravenously administered chemotherapeutic agents that are metabolized by CYP3A4 was higher when AKYNZEO capsules was co-administered in cancer patients than when palonosetron alone was co-administered (see Table 12).

Table 12: Effect of a Single Dose of Oral AKYNZEO on the Systemic Exposure of Co-administered Chemotherapy Agents Metabolized by CYP3A4 in Patients with Cancer

Co-administered Chemotherapeutic Agent[a]	**Change in Systemic Exposures of Chemotherapeutic Agents when Co-administered with AKYNZEO Capsules Compared to Co-administration with Palonosetron**	
	AUC_{0-t}[b]	**C_{max}**
Docetaxel 75 to 100 mg/m^2	35%↑	49%↑
Etoposide 35 to 100 mg/m^2	28%↑	10%↑
Cyclophosphamide 500 to 1000 mg/m^2	20%↑	27%↑

[a] Following a single oral dose of AKYNZEO compared to co-administered with palonosetron alone
[b] AUC_{0-t}: AUC from time zero to time t of last measurable concentration
↑ = Increased; ↓ = Decreased

The mean AUCinf of palonosetron was about 65% higher when AKYNZEO capsules was co-administered with docetaxel than with etoposide or cyclophosphamide, while the mean

AUCinf of netupitant was similar among groups that received docetaxel, etoposide, or cyclophosphamide *[see Drug Interactions (7.1)]*.

Erythromycin

When 500 mg erythromycin was co-administered with netupitant 300 mg, the systemic exposure of erythromycin was highly variable and the mean Cmax and AUCinf of erythromycin were increased by 92% and 56%, respectively. The change in exposure is not clinically significant.

Oral Contraceptives

A single dose of AKYNZEO capsules, when given with a single oral dose of 60 mcg ethinyl estradiol and 300 mcg levonorgestrel, showed no effect on Cmax and increased the AUC0-t of levonorgestrel by 46%. The Cmax and AUC0-t of ethinyl estradiol increased by 5% and 16% respectively. The change in exposure is not clinically significant *[see Drug Interactions (7.1)]*.

Other CYP P450 enzymes

Based on the *in vitro* studies, netupitant, and its metabolites are unlikely to have *in vivo* drug-drug interaction via inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 at the clinical dose of oral AKYNZEO.

Netupitant and its metabolites, M1, M2 and M3, are not inducers of CYP1A2, CYP2B6, CYP2C9, CYP2C19 and CYP3A4.

In *in vitro* studies, palonosetron did not inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2D6, CYP2E1 and CYP3A4/5 or induce CYP1A2, CYP2D6 or CYP3A4/5. CYP2C19 was not investigated.

Transporters – P-gp and BCRP

Based on *in vitro* studies, netupitant is an inhibitor of P-glycoprotein (P-gp) and breast cancer resistant protein (BCRP) transporters. *In vitro* studies indicated that fosnetupitant is an inhibitor of P-gp. However, an *in vivo* interaction between AKYNZEO for injection and P-gp substrates is considered unlikely.

In vitro, palonosetron was an inhibitor of MATE1, MATE2-K, OCT1, OCT2 and OAT3 transporters. An *in vivo* interaction between AKYNZEO capsules or injection and transporter substrates is considered unlikely.

Digoxin –P-gp Substrate

Co-administration of oral netupitant 450 mg (1.5 times the recommended dose in AKYNZEO capsules) did not significantly affect the systemic exposure (4% increase of AUC_{0-24} at steady state) and urinary excretion (2% increase) of oral digoxin, a substrate of P-gp, at steady-state. Concurrent administration of AKYNZEO capsules or AKYNZEO for injection with digoxin is not expected to affect the systemic exposure to digoxin.

Other Transporters

In vitro studies indicate that netupitant and its three major metabolites are unlikely to have *in vivo* drug-drug interactions with human efflux transporters BSEP, MRP2, and human uptake

transporters OATP1B1, OATP1B3, OAT1, OAT3, OCT1, and OCT2 at the clinical dose of 300 mg.

In vitro studies indicated that fosnetupitant is an inhibitor of OATP1B1 and OATP1B3 transporters. However, an *in vivo* interaction between AKYNZEO for injection and OATP1B1, OATP1B3, and P-gp substrates is considered unlikely.

Effects of Other Drugs on Netupitant/Fosnetupitant and/or Palonosetron

Netupitant is not a substrate for P-gp. However, metabolite M2 is a substrate for P-gp.

Netupitant and palonosetron are CYP3A4 substrates. Co-administration of strong CYP3A4 inhibitors, such as ketoconazole, or strong CYP3A4 inducers, such as rifampin, with a single oral administration of AKYNZEO capsules affects with clinical significance the exposure to netupitant but not to palonosetron (Table 13).

Table 13: Change in Systemic Exposure to Netupitant and Palonosetrona When a Single Dose of AKYNZEO is Co-Administered with Either a CYP3A4 Inhibitor or a CYP3A4 Inducer in Healthy Subjects

Co-administered Drug	Netupitant[b]		Palonosetron[b]	
	AUC_{inf}	C_{max}	AUC_{inf}	C_{max}
Strong CYP3A4 Inhibitor				
Ketoconazole 400 mg once daily for 12 days	140%↑	25%↑	10%↑	15%↑
Strong CYP3A4 Inducer				
Rifampin 600 mg once daily for 17 days	62%↓	82%↓	19%↓	15%↓

[a] Following a single oral dose of AKYNZEO; [b] Geometric Mean AUC_{inf} and C_{max}; ↑ = Increased; ↓ = Decreased

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Netupitant

Long-term studies in animals to evaluate carcinogenic potential have not been performed with netupitant. Netupitant was not genotoxic in the Ames test, the mouse lymphoma cell mutation test, or the *in vivo* rat micronucleus test.

Daily oral administration of netupitant in rats at doses up to 30 mg/kg (1.9 times the human AUC in male rats and 3.7 times the human AUC in female rats at the recommended dose) had no effects on fertility or reproductive performance.

Fosnetupitant

Long-term studies in animals to evaluate carcinogenic potential have not been performed with fosnetupitant.

Fosnetupitant was not genotoxic in the Ames test and *in vivo* rat micronucleus test. In human lymphocytes, fosnetupitant did not induce structural chromosomal aberrations.

Daily intravenous administration of fosnetupitant in rats at doses up to 39 mg/kg (1.3 times the human AUC for fosnetupitant and 4.3 times the human AUC for netupitant at the recommended single dose to be given with each cycle of chemotherapy) had no effects on fertility or reproductive performance.

Palonosetron

In a 104-week carcinogenicity study in CD-1 mice, animals were treated with oral doses of palonosetron at 10, 30, and 60 mg/kg/day. Treatment with palonosetron was not tumorigenic. The highest tested dose produced a systemic exposure to palonosetron (plasma AUC) of about 90 to 173 times the human exposure (AUC=49.7 ng•h/mL) at the recommended oral dose of 0.5 mg. In a 104-week carcinogenicity study in Sprague-Dawley rats, male and female rats were treated with oral doses of 15, 30, and 60 mg/kg/day and 15, 45, and 90 mg/kg/day, respectively. The highest doses produced a systemic exposure to palonosetron (plasma AUC) of 82 and 185 times the human exposure at the recommended dose. Treatment with palonosetron produced increased incidences of adrenal benign pheochromocytoma and combined benign and malignant pheochromocytoma, increased incidences of pancreatic Islet cell adenoma and combined adenoma and carcinoma and pituitary adenoma in male rats. In female rats, it produced hepatocellular adenoma and carcinoma and increased the incidences of thyroid C-cell adenoma and combined adenoma and carcinoma.

Palonosetron was not genotoxic in the Ames test, the Chinese hamster ovarian cell (CHO/HGPRT) forward mutation test, the ex vivo hepatocyte unscheduled DNA synthesis (UDS) test, or the mouse micronucleus test. It was, however, positive for clastogenic effects in the Chinese hamster ovarian (CHO) cell chromosomal aberration test. Palonosetron at oral doses up to 60 mg/kg/day (about 921 times the recommended oral dose based on body surface area) was found to have no effect on fertility and reproductive performance of male and female rats.

14 CLINICAL STUDIES

Study 1

In a multicenter, randomized, parallel, double-blind, controlled clinical trial of 694 patients, the efficacy and safety of a single dose of oral netupitant in combination with oral palonosetron was compared with a single oral dose of palonosetron in cancer patients receiving a chemotherapy regimen that included cisplatin (median dose of 75 mg/m^2). The efficacy of AKYNZEO was assessed in 135 patients who received AKYNZEO capsules (300 mg netupitant and 0.5 mg palonosetron) and 136 patients who received oral palonosetron 0.5 mg.

Treatment regimens for the AKYNZEO and palonosetron arms are summarized in Table 14.

Table 14: Oral Antiemetic Treatment Regimen in Study 1

Treatment Regimen	Day 1	Days 2 to 4
AKYNZEO	AKYNZEO capsules: 300 mg neupitant/ 0.5 mg palonosetron Dexamethasone 12 mg	Dexamethasone 8 mg once a day
Palonosetron	Palonosetron 0.5 mg Dexamethasone 20 mg	Dexamethasone 8 mg twice a day

Of the 135 patients who received AKYNZEO, 43% were women, and all patients were White. The age ranged from 19 to 77 years, with a median age of 53 years.

During the study, 86% of the 135 treated patients in the AKYNZEO arm received a concomitant chemotherapeutic agent in addition to protocol-mandated cisplatin. The most common chemotherapeutic agents and the proportion of patients exposed were cyclophosphamide (34%), fluorouracil (24%), etoposide (21%), and doxorubicin (16%).

The key efficacy endpoints were complete response (CR) (defined as no emetic episode and no use of rescue medication) for the 25 to 120 hour interval (delayed phase), CR for the 0 to 24 hour interval (acute phase), and CR within 120 hours (overall phase) after the start of the chemotherapy administration.

A summary of the key results from this study is shown in Table 15.

Table 15: Proportion of Patients Responding by Treatment Group and Phase in Study 1

	AKYNZEO Capsules 300 mg netupitant/ 0.5 mg palonosetron N=135	**Palonosetron 0.5 mg N=136**	
	%	**%**	**p-value***
COMPLETE RESPONSE			
Delayed Phase†	90.4	80.1	0.032
Acute Phase‡	98.5	89.7	0.002
Overall Phase§	89.6	76.5	0.003

*Adjusted p-values for multiple comparisons using Cochran-Mantel-Haenszel test, stratified by gender.
†Delayed phase: 25 to 120 hours post-cisplatin treatment.
‡Acute phase: 0 to 24 hours post-cisplatin treatment.
§Overall: 0 to 120 hours post-cisplatin treatment.

Study 2 (NCT01339260)

In a multicenter, randomized, parallel, double-blind, active controlled, superiority trial, the efficacy and safety of a single oral dose of AKYNZEO was compared with a single oral dose of palonosetron 0.5 mg in cancer patients scheduled to receive the first cycle of an anthracycline and cyclophosphamide (AC) regimen for the treatment of a solid malignant tumor (Study 2). All patients received a single oral dose of dexamethasone. Treatment regimens for the AKYNZEO and palonosetron arms are summarized in Table 16.

Table 16: Oral Antiemetic Treatment Regimen in Study 2

Treatment Regimen	Day 1	Days 2 to 3
AKYNZEO	AKYNZEO capsules: 300 mg netupitant/ 0.5 mg palonosetron Dexamethasone 12 mg	No antiemetic treatment
Palonosetron	Palonosetron 0.5 mg Dexamethasone 20 mg	No antiemetic treatment

After completion of cycle 1, patients had the option to participate in a multiple-cycle extension, receiving the same treatment as assigned in cycle 1. There was no pre-specified limit of the number of repeat consecutive cycles for any patient.

A total of 1455 patients were randomized to the AKYNZEO arm or palonosetron arm. A total of 1450 patients (AKYNZEO n=725; palonosetron n=725) received study medication: of these, 1438 patients (99%) completed cycle 1 and 1286 patients (88%) continued treatment in the multiple-cycle extension. A total of 907 patients (62%) completed the multiple-cycle extension up to a maximum of eight treatment cycles.

Of the 725 patients who received AKYNZEO, 711 (98%) were women; 79% were White, 14% Asian, 6% Hispanic, and <1% were Black or Other. Age ranged from 22 to 79 years, with a median age of 54 years. A total of 724 patients (99.9%) were treated with cyclophosphamide. All patients were additionally treated with either doxorubicin (68%) or epirubicin (32%).

During the first cycle, 32% of the 725 patients treated with AKYNZEO received a concomitant chemotherapeutic agent in addition to protocol-mandated regimens, with the most common chemotherapeutic being fluorouracil (28%) and docetaxel (3%).

The primary efficacy endpoint was the CR rate in the delayed phase, 25 to120 hours after the start of chemotherapy administration.

Major secondary efficacy endpoints included CR for the acute and overall phases. A summary of key results from Study 2 is shown in Table 17.

Table 17: Proportion of Patients Responding by Treatment Group and Phase – Cycle 1 in Study 2

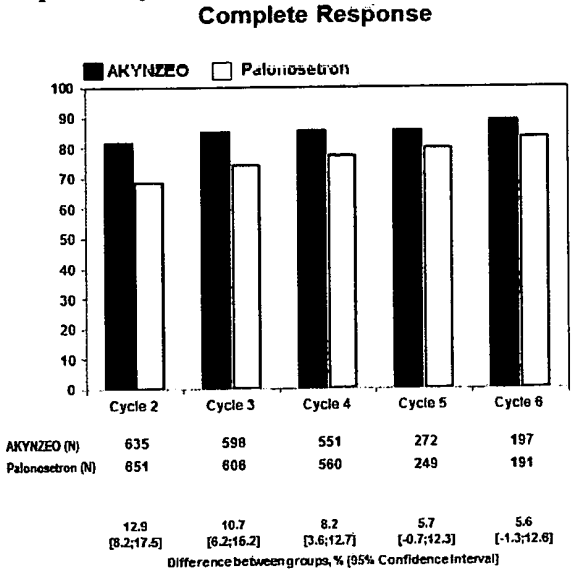
	AKYNZEO Capsules 300 mg netupitant/ 0.5 mg palonosetron N=724 %	Palonosetron 0.5 mg N=725 %	p-value*
PRIMARY ENDPOINT			
COMPLETE RESPONSE			
Delayed Phase†	76.9	69.5	0.001
MAJOR SECONDARY ENDPOINTS			
COMPLETE RESPONSE			
Acute Phase‡	88.4	85.0	0.047
Overall Phase§	74.3	66.6	0.001

*p-value from Cochran-Mantel-Haenszel test, stratified by age class and region.
‡Acute phase: 0 to 24 hours after anthracycline and cyclophosphamide regimen.
†Delayed phase: 25 to 120 hours after anthracycline and cyclophosphamide regimen.
§Overall: 0 to 120 hours after anthracycline and cyclophosphamide regimen.

Multiple Cycles

Patients continued into the Multiple-Cycle extension for up to 7 additional cycles of chemotherapy. The proportion of patients with complete response in the delayed phase by treatment group at each cycle (cycles 2 to 6) is displayed in Figure 1. A limited number of patients received treatment beyond cycle 6. During all cycles the CR rate in the delayed phase was higher for AKYNZEO than for palonosetron. Antiemetic activity of AKYNZEO was maintained throughout repeat cycles for those patients continuing in each of the multiple cycles.

Figure 1: Proportion of Patients with Complete Response in the Delayed Phase by Treatment Group and Cycle in Study 2



Additional clinical trials (Study 3 and Study 4) were conducted to support the efficacy of AKYNZEO.

Study 3 (NCT01376297)

In a separate study, 309 patients undergoing initial and repeat cycles of chemotherapy (including carboplatin, cisplatin, oxaliplatin, and doxorubicin regimens) received AKYNZEO; efficacy was maintained throughout all cycles.

Study 4 (NCT01363479)

In a multicenter, multinational, randomized, active-controlled, double-blind, double-dummy, parallel group, clinical non-inferiority study, the efficacy and safety of a single dose of oral palonosetron 0.5 mg was compared to intravenous palonosetron 0.25 mg in cancer patients scheduled to receive highly emetogenic cisplatin ($\geq$70 mg/m^2) based chemotherapy. The purpose of this study was to demonstrate that oral palonosetron 0.5 mg contributes to the efficacy of AKYNZEO during the acute phase (first 24 hours after cancer chemotherapy) in the setting of cisplatin based chemotherapy. A total of 739 patients (oral palonosetron n=370; intravenous palonosetron n=369) received study medication.

The primary efficacy endpoint was complete response (CR) (defined as no emetic episode and no use of rescue medication) within 24 hours (acute phase) after the start of cisplatin-based chemotherapy administration. In the oral palonosetron arm, 89.4% of patients achieved a CR in the acute phase compared to 86.2% of patients in the intravenous palonosetron arm, with a difference of 3.2% (99% CI: -2.7% to 9.2%). Non-inferiority of oral palonosetron versus intravenous palonosetron was demonstrated since the lower limit of the two-sided 99% CI for the difference in proportions of patients with CR was greater (i.e., closer to zero) than the pre-defined non-inferiority margin set at -15%.

Study 5 (NCT02557035)

In a multicenter, multinational, randomized, active controlled, double blind, double dummy, parallel group, clinical non-inferiority study, the efficacy and safety of a single dose of intravenous palonosetron 0.25 mg administered over 30 minutes (infusion) was compared to intravenous palonosetron 0.25 mg administered over 30 seconds (bolus) in cancer patients scheduled to receive a HEC chemotherapy regimen that included cisplatin administered as a single IV dose of 70 mg/m^2, cyclophosphamide 1500 mg/m^2, carmustine (BCNU) >250mg/m^2, dacarbazine (DTIC) and mechloretamine (nitrogen mustard). The purpose of this study was to demonstrate that intravenous palonosetron 0.25 mg administered over 30 minutes was non-inferior to administration of intravenous palonosetron 0.25 mg administered over 30 seconds for prevention of nausea and vomiting during the acute phase (first 24 hours after cancer chemotherapy) in the HEC setting. A total of 425 patients (intravenous palonosetron infusion n=214; intravenous palonosetron bolus n=211) received study medication and HEC and completed the 0-24 h study period with no major protocol violations and were included in the Per Protocol Population.

The primary efficacy endpoint was complete response (CR defined as no emetic episode and no use of rescue medication) in the 24 hours (acute phase) after the start of the scheduled chemotherapy. In the intravenous palonosetron infusion group, 82.7% of patients achieved CR in the acute phase compared to 86.3% of patients in the intravenous palonosetron bolus group, with a difference of -3.4% (99% CI: - 12.0% to 5.2%). Non-inferiority of administration of

intravenous palonosetron over 30 minutes compared to administration of intravenous palonosetron over 30 seconds was demonstrated since the lower limit of the two-sided 99% CI for the difference in proportions of patients with CR was greater (i.e., closer to zero) than the pre-defined non inferiority margin set at -15%.

16 HOW SUPPLIED/STORAGE AND HANDLING

Capsules

AKYNZEO (300 mg netupitant/0.5 mg palonosetron) capsules: hard gelatin capsules with white body and caramel cap with "HE1" printed on the body. They are supplied as follows:

NDC # 69639-101-01: pack of one capsule in one blister

NDC # 69639-101-04: pack of four capsules (two capsules per blister strip).

Storage

AKYNZEO capsules should be stored at 20 °C to 25 °C (68 °F to 77 °F); excursions permitted from 15 °C to 30 °C (59 °F to 86 °F) [see USP Controlled Room Temperature].

For Injection

AKYNZEO (235 mg fosnetupitant/0.25 mg palonosetron) for injection: sterile, white to off-white lyophilized powder in single-dose vial for reconstitution.

NDC # 69639-102-01: pack of one vial

Storage

AKYNZEO for injection should be stored in carton, protected from light at 2° to 8°C (35.6 F to 46.4°F).

17 PATIENT COUNSELING INFORMATION

Advise patients to read the FDA-approved patient labeling (Patient Information).

Administration

Advise patients to take AKYNZEO capsules with or without food approximately 1 hour prior to the start of chemotherapy *[see Dosage and Administration (2.1)]*.

Hypersensitivity Reactions

Advise patients that hypersensitivity reactions, including anaphylaxis, may occur in patients receiving AKYNZEO. Advise patients to seek immediate medical attention if any signs or symptoms of a hypersensitivity reaction occur while taking AKYNZEO *[See Warnings and Precautions (5.1)]*.

Serotonin Syndrome

Advise patients of the possibility of serotonin syndrome, especially with concomitant use of AKYNZEO and another serotonergic agent such as medications to treat depression and migraines. Advise patients to seek immediate medical attention if the following symptoms occur: changes in mental status, autonomic instability, neuromuscular symptoms, with or without gastrointestinal symptoms [see Warnings and Precautions (5.2)].

Pregnancy

Inform female patients of reproductive potential that AKYNZEO may cause fetal harm and to inform their prescriber of a known or suspected pregnancy [see Use in Specific Populations (8.1)].

Manufactured by Helsinn Birex Pharmaceuticals, Dublin, Ireland for Helsinn Healthcare SA, Switzerland

Distributed by Helsinn Therapeutics (U.S.), Inc., Iselin, NJ 08830, under license of Helsinn Healthcare SA, Switzerland

AKYNZEO is a registered trademark of Helsinn Healthcare SA, Lugano, Switzerland

Patient Information

AKYNZEO® (a kin zee oh)

(netupitant and palonosetron) capsules, for oral use

(fosnetupitant and palonosetron) for injection, for intravenous use

Read this Patient Information before you start receiving AKYNZEO and each time you are scheduled to receive AKYNZEO. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment.

What is AKYNZEO?

AKYNZEO is a prescription medicine called an "antiemetic." AKYNZEO is used in combination with the medicine dexamethasone in people to help prevent the nausea and vomiting that happens right away or later with certain anti-cancer medicines (chemotherapy).

It is not known if AKYNZEO is safe and effective in children under 18 years of age.

Before you take or receive AKYNZEO, tell your doctor about all of your medical conditions, including if you:

- have had an allergic reaction to palonosetron or another medicine for nausea or vomiting.
- have liver problems.
- have kidney problems.
- are pregnant or plan to become pregnant. AKYNZEO may harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if AKYNZEO passes into your breast milk. You and your doctor should decide if you will take AKYNZEO or breastfeed. You should not do both.

Tell your doctor about all of the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

AKYNZEO and certain other medicines can affect each other, causing serious side effects.

How will I take or receive AKYNZEO?

- Take AKYNZEO exactly as your doctor tells you to take it.
- Take 1 AKYNZEO capsule by mouth, about 1 hour before you get your anti-cancer medicine (chemotherapy).
- AKYNZEO for injection will be given to you in your vein by I.V. (intravenous) infusion about 30 minutes before you start your chemotherapy treatment.
- Take AKYNZEO capsule with or without food.
- If you take too much AKYNZEO, call your doctor or go to the nearest hospital emergency room right away.

What are the possible side effects of AKYNZEO?

AKYNZEO may cause serious side effects, including:

- **allergic reactions**, such as anaphylaxis. Get emergency medical help right away if you get any of the following symptoms of a serious allergic reaction with AKYNZEO: hives, swollen face, trouble breathing, or chest pain.
- **serotonin syndrome** which can happen with AKYNZEO particularly with certain other medicines such as anti-depressants and anti-migraine medicines and can lead to death.
    - **Stop taking AKYNZEO capsules and go to the nearest hospital emergency room right away if you get any of the following symptoms of serotonin syndrome**: agitation, hallucinations or other changes in mental status, dizziness, fast heartbeat, sweating, low body temperature, shaking (tremors), unsteady movements, muscle twitching (overactive reflexes), or seizures with or without nausea, vomiting, and diarrhea.

The most common side effects of AKYNZEO capsules and injection include: headache, weakness, fatigue, upset stomach, constipation, and skin redness.

These are not all the possible side effects of AKYNZEO. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store AKYNZEO capsules?

Store AKYNZEO at room temperature between 68°F to 77°F (20°C to 25°C).

General information about the safe and effective use of AKYNZEO

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use AKYNZEO for a condition for which it was not prescribed. Do not give AKYNZEO to other people, even if they have the same symptoms that you have. It may harm them. You can ask your doctor or pharmacist for information about AKYNZEO that is written for health professionals.

What are the ingredients in AKYNZEO capsules?

Active ingredients: netupitant and palonosetron hydrochloride

Inactive ingredients: butylated hydroxyanisole (BHA), croscarmellose sodium, gelatin, glycerin, magnesium stearate, microcrystalline cellulose, mono- and di-glycerides of capryl/capric acid, polyglyceryl dioleate, povidone K-30, purified water, red iron oxide, silicon dioxide, sodium stearyl fumarate, sorbitol, sucrose fatty acid esters, titanium dioxide and yellow iron oxide. It may contain traces of medium-chain triglycerides, lecithin, and denatured ethanol. AKYNZEO may contain small amounts of medium-chain triglycerides, lecithin, and denatured ethanol.

What are the ingredients in AKYNZEO for injection?

Active ingredients: fosnetupitant chloride hydrochoride and palonosetron hydrochloride

Inactive ingredients: mannitol, edetate disodium, sodium hydroxide, and hydrochloric acid may be added for pH adjustment.

Manufactured by Helsinn Birex Pharmaceuticals, Dublin, Ireland
for Helsinn Healthcare SA, Switzerland
Distributed by Helsinn Therapeutics (U.S.), Inc. Iselin, NJ 08830 under license of Helsinn Healthcare SA, Switzerland
AKYNZEO is a registered trademark of Helsinn Healthcare SA, Lugano, Switzerland
For more information, go to www.akynzeo.com

This Patient Information has been approved by the U.S. Food and Drug Administration. Approved: April 2018

APPENDIX C

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 210493

NDA APPROVAL

Helsinn Healthcare SA
c/o August Consulting, Inc.
Attention: Craig Lehmann, PharmD.
Authorized Representative
515 Capital of Texas Highway, Suite 150
Austin, TX 78746

Dear Dr. Lehmann:

Please refer to your New Drug Application (NDA) dated April 20, 2017, received April 20, 2017, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Akynzeo (fosnetupitant and palonosetron) injection, 235 mg/0.25 mg.

This new drug application provides for the use of Akynzeo (fosnetupitant and palonosetron) injection for prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

WAIVER OF HIGHLIGHTS SECTION

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the prescribing information, text for the patient package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the enclosed carton and immediate container labels and carton and immediate container labels submitted on December 14, 2017 and March 12, 2018, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (May 2015, Revision 3)*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 210493.**" Approval of this submission by FDA is not required before the labeling is used.

ADVISORY COMMITTEE

Your application for Akynzeo (fosnetupitant and palonosetron) injection was not referred to an FDA advisory committee because the application did not raise significant safety or efficacy issues that were unexpected for a drug of this class.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are deferring submission of your pediatric studies until December 2024, because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required under section 505B(a) of the Federal Food, Drug, and Cosmetic Act are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(C) of the Federal Food, Drug, and Cosmetic Act. These required studies are listed below.

3292-1 An 8-week GLP toxicology study with fertility evaluation in neonatal rats treated with fosnetupitant (pro-netupitant) alone.

Final Protocol Submission:	06/2020
Study Completion:	06/2021
Final Report Submission:	09/2021

3292-2 An open-label, pharmacokinetic and safety study of intravenous fosnetupitant/ palonosetron combination in pediatric cancer patients ages 0-17 years for the prevention of nausea and vomiting associated with emetogenic chemotherapy.

Final Protocol Submission:	01/2022
Study Completion:	07/2024
Final Report Submission:	12/2024

Submit the protocol(s) to your IND 115191, with a cross-reference letter to this NDA.

Reports of these required pediatric postmarketing studies must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

3292-3 *In vitro* study to evaluate the inhibition potential of fosnetupitant towards MATE2-K.

The timetable you submitted on January 10, 2018, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	10/2018
Final Protocol Submission:	01/2019
Study Completion:	01/2020
Final Report Submission:	07/2020

3292-4 *In vitro* study to evaluate the potential of fosnetupitant to be a substrate for P-gp/MDR1, BCRP, BSEP, MATE1, MATE2-K, OAT1, OAT3, OCT1, and OCT2.

The timetable you submitted on January 10, 2018, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	10/2018
Final Protocol Submission:	01/2019
Study Completion:	01/2020
Final Report Submission:	07/2020

Submit clinical protocols to your IND 115191 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled **"Postmarketing Commitment Protocol," "Postmarketing Commitment Final Report," or "Postmarketing Commitment Correspondence."**

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the prescribing information, Medication Guide, and patient PI (as applicable) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the prescribing information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Mary Chung, Regulatory Project Manager, at (301) 796-0260.

Sincerely,

{See appended electronic signature page}

Julie Beitz, M.D.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure(s):
Content of Labeling
Carton and Container Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JULIE G BEITZ
04/19/2018

APPENDIX D

US009186357B2

(12) **United States Patent**
Trento et al.

(10) **Patent No.: US 9,186,357 B2**
(45) **Date of Patent: *Nov. 17, 2015**

(54) **COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING**

(71) Applicant: **Helsinn Healthcare S.A.**, Lugano/Pazzallo (CH)

(72) Inventors: **Fabio Trento**, Como (IT); **Sergio Cantoreggi**, Cagiallo (CH); **Giorgia Rossi**, Como (IT); **Roberta Cannella**, Varese (IT); **Daniele Bonadeo**, Varese (IT)

(73) Assignee: **HELSINN HEALTHCARE SA**, Lugano/Pazzallo (CH)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **14/069,927**

(22) Filed: **Nov. 1, 2013**

(65) **Prior Publication Data**

US 2014/0194395 A1 Jul. 10, 2014

Related U.S. Application Data

(63) Continuation of application No. 13/077,462, filed on Mar. 31, 2011, now Pat. No. 8,623,826, which is a continuation of application No. PCT/IB2010/003106, filed on Nov. 18, 2010.

(60) Provisional application No. 61/262,470, filed on Nov. 18, 2009, provisional application No. 61/382,709, filed on Sep. 14, 2010.

(51) **Int. Cl.**

A61K 31/496	(2006.01)
A61K 31/573	(2006.01)
A61K 31/473	(2006.01)
A61K 9/48	(2006.01)
A61K 31/4178	(2006.01)
A61K 45/06	(2006.01)
A61K 9/20	(2006.01)
A61K 9/00	(2006.01)

(52) **U.S. Cl.**

CPC ***A61K 31/496*** (2013.01); ***A61K 9/0053*** (2013.01); ***A61K 9/2054*** (2013.01); ***A61K 9/4808*** (2013.01); ***A61K 9/4858*** (2013.01); ***A61K 31/4178*** (2013.01); ***A61K 31/473*** (2013.01); ***A61K 31/573*** (2013.01); ***A61K 45/06*** (2013.01); ***Y10S 514/872*** (2013.01)

(58) **Field of Classification Search**

USPC 514/17.7

See application file for complete search history.

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(Continued)

Primary Examiner — Walter Webb

(74) *Attorney, Agent, or Firm* — Troutman Sanders LLP

(57) **ABSTRACT**

Provided are compositions and methods for treating or preventing nausea and vomiting in patients undergoing chemotherapy, radiotherapy, or surgery.

62 Claims, 5 Drawing Sheets

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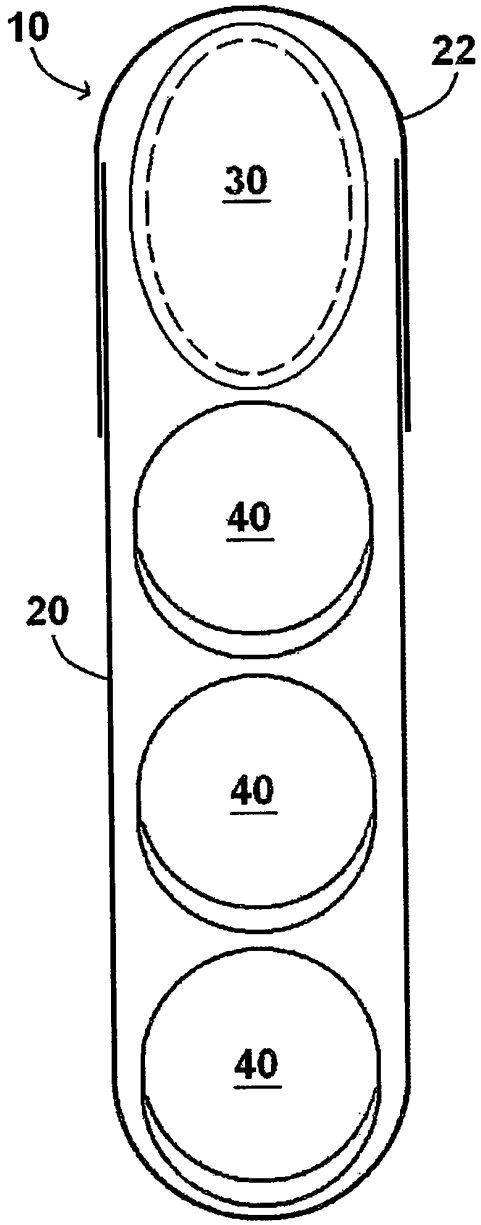


Figure 1

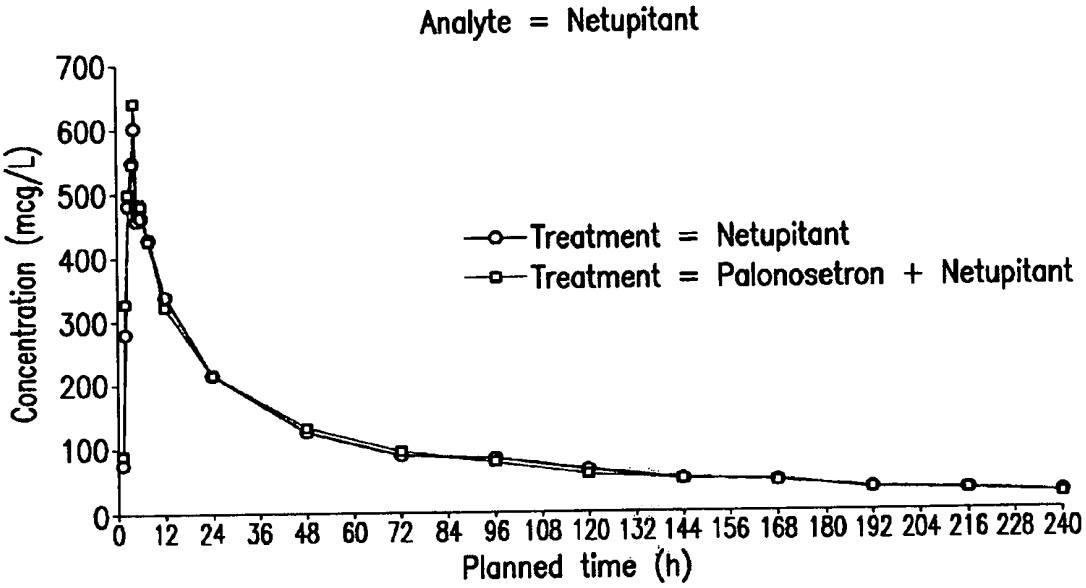

Analyte = Netupitant
Concentration (mcg/L)
700
600
500
400
300
200
100
0
0 12 24 36 48 60 72 84 96 108 120 132 144 156 168 180 192 204 216 228 240
Planned time (h)
Treatment = Netupitant
Treatment = Palonosetron + Netupitant

FIG.2

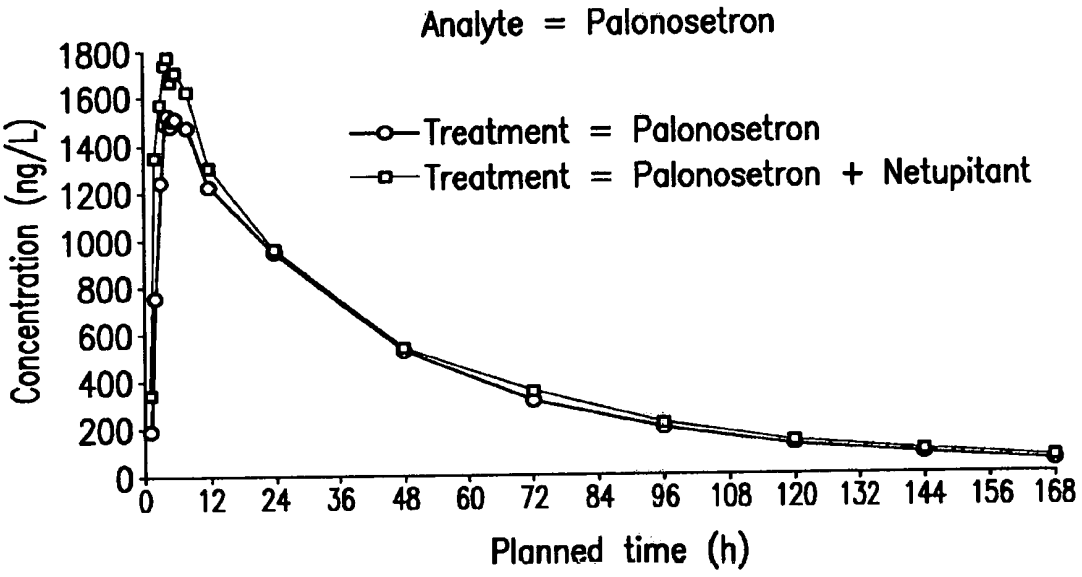

Analyte = Palonosetron
Treatment = Palonosetron
Treatment = Palonosetron + Netupitant
Concentration (ng/L)
1800
1600
1400
1200
1000
800
600
400
200
0
0
12
24
36
48
60
72
84
96
108
120
132
144
156
168
Planned time (h)

FIG.3

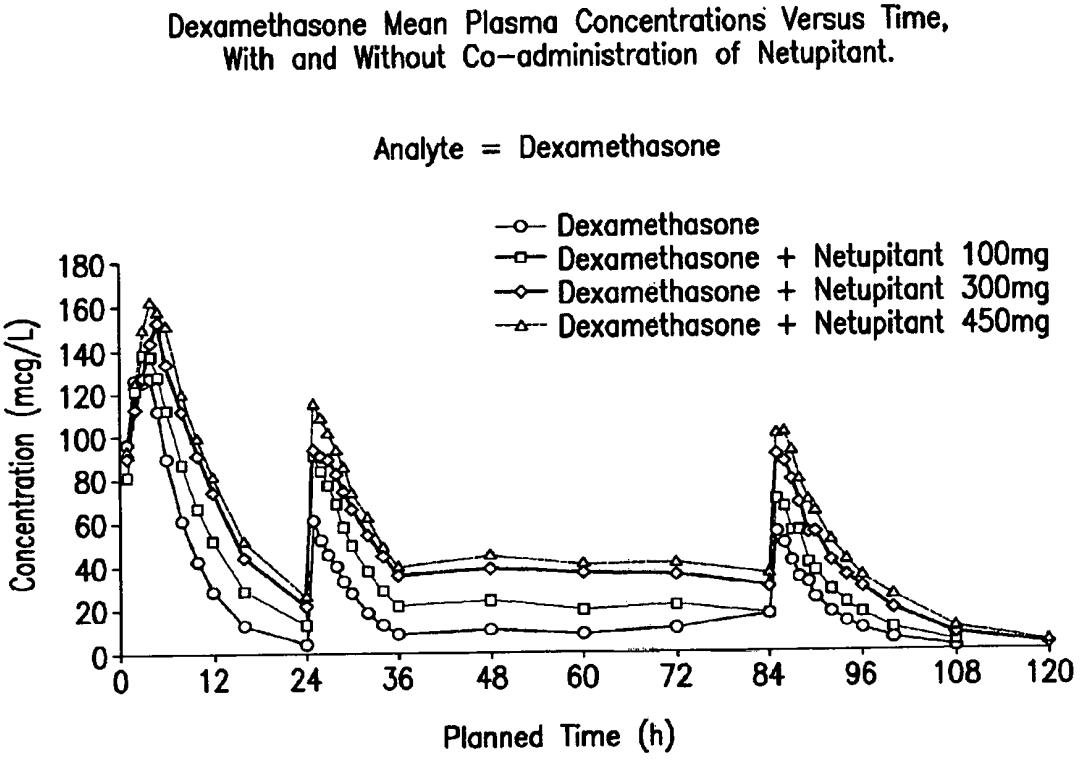

Dexamethasone Mean Plasma Concentrations Versus Time,
With and Without Co-administration of Netupitant.
Analyte = Dexamethasone
Dexamethasone
Dexamethasone + Netupitant 100mg
Dexamethasone + Netupitant 300mg
Dexamethasone + Netupitant 450mg
Concentration (mcg/L)
180
160
140
120
100
80
60
40
20
0
0
12
24
36
48
60
72
84
96
108
120
Planned Time (h)

FIG.4

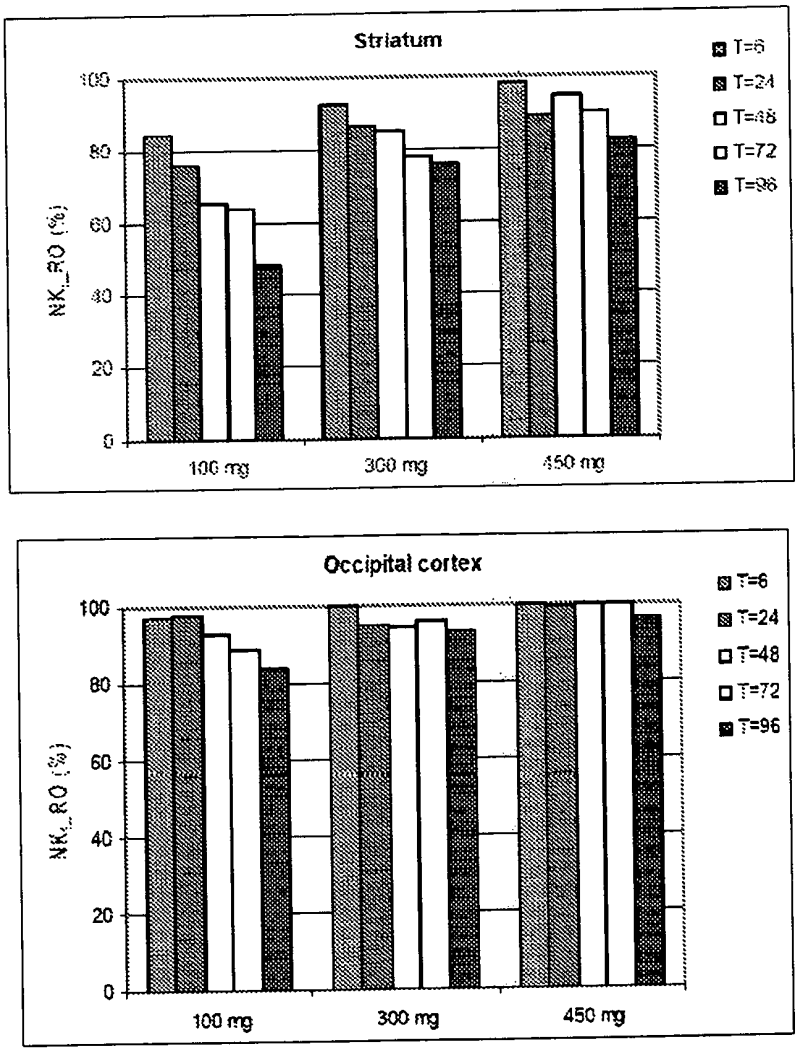

Striatum
T=6
T=24
T=48
T=72
T=96
NK_RO (%)
100
80
60
40
20
0
100 mg
300 mg
450 mg
Occipital cortex
T=6
T=24
T=48
T=72
T=96
NK_RO (%)
100
80
60
40
20
0
100 mg
300 mg
450 mg

FIG. 5

COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. application Ser. No. 13/077,462, filed Mar. 31, 2011, which is a continuation of International Application No. PCT/IB2010/003106, filed Nov. 18, 2010, which claims priority to U.S. Provisional Application No. 61/262,470, filed Nov. 18, 2009, and U.S. Provisional Application No. 61/382,709, filed Sep. 14, 2010. All of the above applications are hereby incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

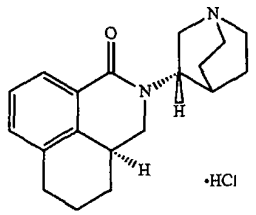
The present invention relates to the use of centrally acting NK_1 antagonists to treat nausea and vomiting, particular nausea and vomiting induced by highly emetogenic chemotherapy, and to the treatment of such nausea and vomiting over multiple consecutive days. The present invention also relates to combined oral dosage forms of palonosetron and netupitant.

BACKGROUND OF THE INVENTION

With the development of the 5-HT_3 antagonist in the early 1990s, there emerged new strategies in the medical community to better control nausea and vomiting caused by various medical procedures, including chemotherapy (CINV), surgery (PONV), and radiation therapy (RINV). When added to steroids such as dexamethasone, several 5-HT_3 antagonists have been demonstrated to significantly improve the standard of life for patients undergoing emetogenic medical procedures. Examples of 5-HT_3 antagonists include ondansetron, marketed by GlaxoSmithKline, and palonosetron, developed by Helsinn Healthcare.

Palonosetron hydrochloride has recently emerged as a highly efficacious anti-nauseant and anti-emetic agent. See PCT publications WO 2004/045615 and 2004/073714 from Helsinn Healthcare. Palonosetron hydrochloride is sold in the United States as a sterile injectable liquid under the ALOXI® brand, in sterile unit dose vials containing 0.075 or 0.25 mg. of palonosetron hydrochloride. Palonosetron hydrochloride also is also sold as an orally administered soft-gel dosage form containing 0.5 mg. of palonosetron hydrochloride.

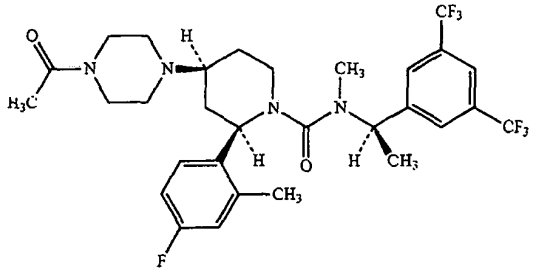
The official chemical name for palonosetron hydrochloride is (3aS)-2-[(S)-1-Azabicyclo[2.2.2]oct-3-yl]-2,3,3a,4,5,6-hexahydro-1-oxo-1Hberiz[de]isoquinoline hydrochloride (CAS No. 119904-90-4); its empirical formula is $C_{19}H_{24}N_2O.HCl$, and its molecular weight is 332.87. The compound is represented by the following chemical structure:



Methods of synthesizing palonosetron are described in U.S. Pat. Nos. 5,202,333 and 5,510,486. Pharmaceutically acceptably dosage forms are described in PCT publications WO 2004/067005 and WO 2008/049552 from Helsinn Healthcare.

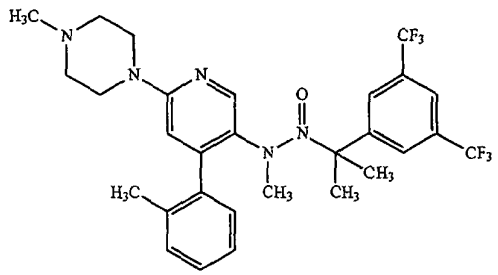
NK_1 antagonists have also recently emerged as a tool for combating nausea and vomiting from emetogenic medical procedures. Most recently, aprepitant was approved by the Food and Drug Administration ("FDA") for use in combination with other anti-emetic agents for the prevention of nausea and vomiting from moderately and highly emetogenic chemotherapy. However, it quickly became apparent that aprepitant's effect was limited principally to vomiting—not nausea—and that aprepitant did not provide as much benefit during the acute phase of CINV. When tested against nausea in humans, aprepitant was unable to induce a significant reduction in the incidence or severity of nausea following moderately or highly emetogenic chemotherapy when compared to a 5-HT_3 antagonist alone. See FDA Approved Labeling for Emend®. Thus, while aprepitant is approved by FDA for the prevention of nausea and vomiting in humans, this indication is somewhat misleading because aprepitant did not reduce nausea in the clinical trials preformed for aprepitant more than nausea controlled by the other components of the anti-emetic regimen. In addition, the results reported in Grunberg et al., SUPPORT CANCER CARE (2009) 17:589-594, from a combined treatment of aprepitant and palonosetron, were far from promising.

Merck & Co. markets aprepitant, as EMEND® in the United States. The product is approved in a capsule dosage form, and is marketed for the prevention of CINV (acute and delayed) in combination with other anti-emetic agents such as ondansetron and metoclopramide. The product reportedly has a terminal half-life of from 9 to 13 hours. While aprepitant has demonstrated some effect against nausea, its effects have been inconsistent. Casopitant is another NK_1 antagonist that has been tested against nausea and vomiting in humans. A clinical study of casopitant is discussed in *Therapeutics and Clinical Risk Management* 2009:5 pp 375-384 to Ruhlmann et al. and *Drug Metabolism and Disposition*, vol. 37, No. 8, 2009, pp. 1635-1645 to Pellegatti et al. As reported by Ruhlmann et al. in THERAPEUTICS AND CLINICAL RISK MANAGEMENT, 2009:5 375-384, casopitant had no statistically significant effect against nausea when administered in response to moderately emetogenic chemotherapy, and even induced nausea as a side effect. Casopitant has the formula (2R,4S)-4-(4-acetylpiperazin-1-yl)-N-{(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethyl}-2-(4-fluoro-2-methylphenyl)-N-methylpiperidine-1-carboxamide, and the below chemical structure:



Netupitant is another selective NK_1 receptor antagonist under development by Helsinn Healthcare, having the formula 2-[3,5-bis(trifluoromethyl)phenyl]-N,2-dimethyl-N-[4-(2-methylphenyl)-6-(4-methylpiperazin-1-yl)pyridin-3-

yl]propanamide, or Benzeneacetamide, N,α,α-trimethyl-N-[4-(2-methylphenyl)-6-(4-methyl-1-piperazinyl)-3-pyridinyl]-3,5-bis(trifluoromethyl)-, and the below chemical structure:



Methods of synthesizing and formulating netupitant and its prodrugs are described in U.S. Pat. Nos. 6,297,375, 6,719,996 and 6,593,472 to Hoffmann La Roche.

Other representative NK_1 antagonists include ZD4974 (developed by AstraZeneca), CGP49823 (developed by Ciba-Geigy), Lanepitant and LY686017 (developed by Eli Lilly), FK888 (developed by Fujisawa), Vofopitant, Vestipitant and Orvepitant (developed by GlaxoSmithKline), Befetupitant (developed by Hoffmann-La Roche), R116031 (developed by Janssen), L-733060 and L-736281 (developed by Merck), TKA731, NKP608 and DNK333 (developed by Novartis), CP-96345, CP-99994, CP-122721, CJ-17493, CJ-11974 and CJ-11972 (developed by Pfizer), RP67580 and Dapitant (developed by Rhone-Poulenc Rorer), Nolpitantium and SSR240600 (developed by Sanofi-Aventis), SCH388714 and Rolapitant (developed by Schering-Plough), TAK637 (developed by Takeda), HSP117 (developed by Hisamitsu), KRP103 (developed by Kyorin Pharm) and SLV317 (developed by Solvay). Chemical structures of the above-mentioned NK_1 antagonists are shown below and discussion of those compounds as well as other NK_1 antagonists is present in *Expert Opin. Ther. Patents* (2010) 20(8), pp 1019-1045 by Huang et al.

The background of U.S. Pat. No. 6,297,375 suggests that NK_1 antagonists are useful for treating a variety of conditions in which substance P (the natural ligand for the NK_1 receptor) is active. These conditions include depression, pain (especially pain resulting from inflammatory conditions such as migraine, rheumatoid arthritis, asthma, and inflammatory bowel disease), central nervous system (CNS) disorders such as Parkinson's disease and Alzheimer's disease, headache, anxiety, multiple sclerosis, attenuation of morphine withdrawal, cardiovascular changes, oedema, chronic inflammatory diseases such as rheumatoid arthritis, asthma/bronchial hyperreactivity and other respiratory diseases including allergic rhinitis, inflammatory diseases of the gut including ulcerative colitis and Crohn's disease, ocular injury and ocular inflammatory diseases. The background even mentions motion sickness and vomiting, but fails to call out nausea specifically.

Accordingly, there is a need in the art for more effective treatments of nausea and vomiting, particularly nausea and vomiting emanating from chemotherapy, radiotherapy and surgery. In addition, given the prolonged incidence of nausea and vomiting induced by these emetic events, there is a need for treating such nausea and vomiting for a prolonged period of time. Further, there is a need for the development of dosage forms to reduce drug-drug interaction, improve stability, and potentiate effects of each component of the combined dosage forms.

OBJECTS OF THE INVENTION

Accordingly, it is an object of the invention to provide new methods for treating or preventing nausea and vomiting using an NK_1 antagonist, particularly netupitant.

It is another object of the invention to provide methods for treating or preventing nausea and vomiting in patients undergoing chemotherapy, radiotherapy, or surgery.

Still another object of the invention is to augment existing treatments for CINV, RINV or PONV by steroids and 5-HT_3 antagonists, and thereby provide additional protection against both nausea and vomiting, especially during the acute and delayed phases.

Another object of the invention is to provide a single combined dose of netupitant and a 5-HT_3 antagonist and to the use of that single dose without further dosing, for the treatment of nausea and vomiting during the acute and delayed phases of CINV, RINV or PONV.

It is another object to provide novel methods to treat nausea, vomiting, and other undesirable effects from moderately emetogenic and highly emetogenic chemotherapy ("MEC and HEC"), especially HEC, during the acute and delayed phases following such treatments.

It is another object to provide novel dosage forms to reduce drug-drug interaction, improve stability, enhance bioavailability and potentiate therapeutic effect of each component of the combined dosage forms comprising netupitant and/or 5-HT_3 antagonist and/or dexamethasone, in treating or preventing nausea and vomiting.

SUMMARY OF THE INVENTION

After extensive testing into the clinical effects of netupitant, it has unexpectedly been discovered that netupitant is active against nausea, and that a single dose of netupitant is able to treat nausea and vomiting in response to highly and moderately emetogenic chemotherapy for five consecutive days. It has also been discovered, quite unexpectedly, that netupitant exhibits unique binding habits to NK_1 receptors in the brain. In particular, it has been discovered that netupitant binds to NK_1 receptors in the striatum in a long-lasting manner, and that less than 20 or 30% of netupitant is released from striatum NK_1 receptors even ninety-six hours after administration. This is in stark contrast to aprepitant, in which receptor binding drops swiftly over time, and must be dosed repeatedly if emesis control is desired throughout the delayed phase; and which shows no meaningful effect against nausea.

These discoveries have led to the development of a unique dosing regimen to treat nausea during the first day after an emesis-inducing event, in addition to the second, third, fourth and fifth days after such induction. Therefore, in one embodiment the invention provides a method of treating nausea and vomiting for a period of five consecutive days in a patient in need thereof, comprising administering to said patient netupitant or a pharmaceutically acceptable salt thereof in an amount which is therapeutically effective against nausea and vomiting during the acute and delayed phases, and which is effective to enter the systemic circulation, cross the blood brain barrier and occupy at least 70% of NK_1 receptors in the striatum seventy-two hours after said administration.

In another embodiment, the netupitant is combined with other anti-emetic agents, including a 5-HT_3 antagonist such as palonosetron and a corticosteroid such as dexamethasone,

in a manner that results in even greater efficacy against nausea. It has been discovered that palonosetron is much more effective in combinations with netupitant than it is in combination with aprepitant, as reported by Grunberg et al., Support Cancer Care (2009) 17:589-594. In addition, palonosetron shows an improved pharmacokinetic profile (e.g., better bioavailability) when palonosetron is in combination with netupitant as opposed to palonosetron in single dose administration. Based on these discoveries, solid oral dosage forms have been developed that combine netupitant or another NK_1 antagonist and palonosetron for the treatment of acute and delayed emesis.

It has also been discovered that netupitant potentiates the effect of dexamethasone, such that the dexamethasone is effective even when administered at sub-therapeutic doses (i.e. doses at which the dexamethasone would be ineffective if administered by itself). Therefore, in another embodiment the invention provides a combination therapy for treating nausea and vomiting for five consecutive days in a patient in need thereof, consisting essentially of:

- Day 1 netupitant—administering to said patient on day one netupinant or a pharmaceutically acceptable salt thereof, in an amount which is therapeutically effective against nausea and vomiting during the acute and delayed phases, and which is effective to enter the systemic circulation, cross the blood brain barrier and occupy at least 70% of NK_1 receptors in the striatum seventy-two hours after said administration;
- Day 1 palonosetron—administering to said patient on day one a therapeutically effective amount of a $5\text{-}HT_3$ antagonist (preferably palonosetron) effective to treat said nausea and vomiting during the acute and delayed phases;
- Day 1 dexamethasone—administering to said patient on day one a first dose of dexamethasone which is ineffective against nausea and vomiting when administered alone, but effective against nausea and vomiting when administered in combination with said netupitant and palonosetron, wherein said first dose comprises from 50 to 70% of a minimum effective dose when administered alone; and
- Days 2-5 dexamethasone—when the patient is undergoing highly emetogenic chemotherapy, administering to said patient, on days two, three and four, a second dose of dexamethasone which is ineffective against nausea and vomiting when administered alone, but effective against nausea and vomiting when administered in combination with said netupitant, wherein said second dose comprises from 40 to 60% of a minimum effective dose when administered alone on days two, three and four.

The dosage forms are extremely versatile and stable owing to their unique design and formulation. This versatility and stability is accomplished by formulating the NK1 antagonist and palonosetron in separate dosage forms and combining the dosage forms in one capsule. Thus, for example, the palonosetron can be formulated in a small gel-cap at a dose of around 0.5 mg, and the netupitant or other NK1 antagonist formulated in a tablet at a dose of about 100 to 150 mg. A capsule can then be filled with one or more palonosetron gel-caps and one or more netupitant (or other NK1 antagonist) tablets, depending on the therapeutic objective for the product. Because the palonosetron and NK1 antagonist are in separate dosage units, they can be formulated without regard to the stability of the other, and without degradation to by-products, for instance (3S)-3-[(3aS)-1-oxo-2,3,3a,4,5,6-hexahydro-1H-benzo[de]isoquinoline-2-yl]-1-azoniabicyclo[2.2.2]octan-1-olate, a degradation by-product of palonosetron. As a result, the presently discovered dosage forms offer advantages, such as, reducing drug-drug interaction, improving stability, and potentiating effects of each component of the dosage forms in treating or preventing emesis.

Thus, in one embodiment the invention provides an orally administered dosage form comprising a combination of palonosetron and an NK1 antagonist (preferably netupitant), or a pharmaceutically acceptable salt or prodrug thereof.

In another embodiment the invention provides an orally administered capsule dosage form comprising (a) an outer shell; (b) one or more tablets housed within said outer shell, each comprising an NK1 antagonist (preferably netupitant) or a pharmaceutically acceptable salt or prodrug thereof and one or more pharmaceutically acceptable excipients; and (c) one or more soft-gel capsules housed within the outer shell, each comprising palonosetron or a pharmaceutically acceptable ester or prodrug thereof and one or more pharmaceutically acceptable excipients; wherein said dosage form comprises (3S)-3-[(3aS)-1-oxo-2,3,3a,4,5,6-hexahydro-1H-benzo[de]isoquinoline-2-yl]-1-azoniabicyclo[2.2.2]octan-1-olate in an amount that does not exceed 3 wt. %.

In still other embodiments the invention provides methods of treating acute and delayed-onset emesis by administering the dosage forms of the present invention to a human in need thereof, preferably shortly before the emesis inducing event.

Additional embodiments and advantages of the invention will be set forth in part in the description which follows, and in part will be obvious from the description, or may be learned by practice of the invention. The embodiments and advantages of the invention will be realized and attained by means of the elements and combinations particularly pointed out in the appended claims. It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as claimed.

BRIEF DESCRIPTION OF THE DRAWINGS

The accompanying drawings, which are incorporated in and constitute a part of this specification, illustrate several embodiments of the invention and together with the description, serve to explain the principles of the invention.

FIG. 1 depicts a capsule containing one soft-gel capsule of palonosetron and three tablets of netupitant.

FIG. 2 is a two dimensional graph plotting the pharmacokinetic profile of netupitant in humans following oral administration of netupitant alone and netupitant together with palonosetron.

FIG. 3 is a two dimensional graph plotting the pharmacokinetic profile of palonosetron in humans following oral administration of palonosetron alone and palonosetron together with netupitant.

FIG. 4 is a two dimensional graph plotting mean plasma concentrations of dexamethasone over time following administration with and without netupitant.

FIG. 5 contains two bar graphs that depict the average NK_1 receptor occupancy at 6, 24, 48, 72 and 96 hours after a single oral dose of 100, 300 and 450 mg. netupitant ($N=2$ for each dose) in striatum and occipital cortex, as measured using positron emission topography.

DETAILED DESCRIPTION OF THE INVENTION

The present invention may be understood more readily by reference to the following definitions and detailed description

of preferred embodiments of the invention and the non-limiting Examples included therein.

Definitions and Use of Terms

When the singular forms "a," "an" and "the" or like terms are used herein, they will be understood to include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a pharmaceutical carrier" includes mixtures of two or more such carriers, and the like. The word "or" or like terms as used herein means any one member of a particular list and also includes any combination of members of that list.

When used herein the term "about" or "ca." will compensate for variability allowed for in the pharmaceutical industry and inherent in pharmaceutical products, such as differences in product strength and bioavailability due to manufacturing variations and time-induced product degradation. The term allows for any variation which in the practice of pharmaceuticals would allow the product being evaluated to be considered pharmaceutically equivalent or bioequivalent, or both if the context requires, to the recited strength of a claimed product.

Throughout the description and claims of this specification, the word "comprise" and variations of the word, such as "comprising" and "comprises," means "including but not limited to," and is not intended to exclude, for example, other additives, components, integers or steps.

As used herein, the term "Pharmaceutically acceptable" means that which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes that which is acceptable for veterinary use as well as human pharmaceutical use. In addition, the term "pharmaceutically acceptable salt" refers to a salt of a compound to be administered prepared from pharmaceutically acceptable non-toxic acids. Examples of suitable inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, sulfuric, and phosphoric. Suitable organic acids may be selected from aliphatic, aromatic, carboxylic and sulfonic classes of organic acids, examples of which are formic, acetic, propionic, succinic, camphorsulfonic, citric, fumaric, gluconic, isethionic, lactic, malic, mucic, tartaric, para-toluenesulfonic, glycolic, glucuronic, maleic, furoic, glutamic, benzoic, anthranilic, salicylic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, pantothenic, benzenesulfonic (besylate), stearic, sulfanilic, alginic, galacturonic, and the like.

Pharmaceutically acceptable salts of palonosetron include palonosetron hydrochloride. Pharmaceutically acceptable pro-drugs of netupitant include those described in U.S. Pat. Nos. 6,593,472, 6,747,026 and 6,806,370, including the N-oxide of netupitant. The contents of these publications are incorporated herein by reference. When a molecule is referred to herein in its base or salt form, it will be understand also to encompass other pharmaceutically acceptable salt forms of the molecule.

As used herein, "therapeutically effective amount" refers to an amount sufficient to elicit the desired biological response. The therapeutically effective amount or dose will depend on the age, sex and weight of the patient, and the current medical condition of the patient. The skilled artisan will be able to determine appropriate dosages depending on these and other factors in addition to the present disclosure.

The minimum effective dose of dexamethasone, when used to treat CINV induced by highly emetogenic chemotherapy, has been demonstrated to be 20 mg. administered orally or by injection on day one, and sixteen mg. administered orally or by injection on days two, three and four. Jordan et al., THE ONCOLOGIST, Vol. 12, No. 9, 1143-1150, September 2007. When used to treat CINV induced by moderately emetogenic chemotherapy, the minimum effective dose of dexamethasone is 20 mg. administered orally or by injection on day one, and zero mg. on days two, three and four.

The terms "treating" and "treatment," when used herein, refer to the medical management of a patient with the intent to cure, ameliorate, stabilize, or prevent a disease, pathological condition, or disorder. This term includes active treatment, that is, treatment directed specifically toward the improvement of a disease, pathological condition, or disorder, and also includes causal treatment, that is, treatment directed toward removal of the cause of the associated disease, pathological condition, or disorder. In addition, this term includes palliative treatment, that is, treatment designed for the relief of symptoms rather than the curing of the disease, pathological condition, or disorder; preventative treatment, that is, treatment directed to minimizing or partially or completely inhibiting the development of the associated disease, pathological condition, or disorder; and supportive treatment, that is, treatment employed to supplement another specific therapy directed toward the improvement of the associated disease, pathological condition, or disorder.

As used herein, the term "significantly" refers to a level of statistical significance. The level of statistical significant can be, for example, of at least $p<0.05$, of at least $p<0.01$, of at least $p<0.005$, or of at least $p<0.001$. Unless otherwise specified, the level of statistical significance is $p<0.05$. When a measurable result or effect is expressed or identified herein, it will be understood that the result or effect is evaluated based upon its statistical significance relative to a baseline. In like manner, when a treatment is described herein, it will be understood that the treatment shows efficacy to a degree of statistical significance.

5-HT_3 antagonists include the various setrons such as, for example, palonosetron, ondansetron, dolasetron, tropisetron, and granisetron, and their pharmaceutically acceptable salts. A preferred 5-HT_3 antagonist is palonosetron, especially its hydrochloride salt.

"Highly emetogenic chemotherapy" refers to chemotherapy having a high degree of emetogenic potential, and includes chemotherapy based on carmustine, cisplatin, cyclophosphamide>1500 mg/m^2, dacarbazine, dactinomycin, mechlorethamine, and streptozotocin.

"Moderately emetogenic chemotherapy" refers to chemotherapy having a moderate degree of emetogenic potential, and includes chemotherapy based on carboplatin, cyclophosphamide<1500 mg/m^2, cytarabine>1 mg/m^2, daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, and oxaliplatin.

Acute emesis refers to the first twenty-four hour period following an emesis-inducing event. Delayed emesis refers to the second, third, fourth and fifth twenty-four hour periods following an emesis-inducing event. When a treatment is said to be effective during the delayed phase, it will be understood to mean that the effectiveness of the treatment is statistically significant during the entire delayed phase, regardless of whether the treatment is effective during any particular twenty-four hour period of the delayed phase. It will also be understood that the method can be defined based upon its effectiveness during any one of the twenty-four hour periods of the delayed phase. Thus, unless otherwise specified, any of the methods of treating nausea and/or vomiting during the delayed phases, as described herein, could also be practiced to treat nausea and/or vomiting during the second, third, fourth or fifth twenty-four hour periods following an emesis inducing event, or an combination thereof.

When ranges are given by specifying the lower end of a range separately from the upper end of the range, it will be understood that the range can be defined by selectively combining any one of the lower end variables with any one of the upper end variables that is mathematically possible.

Methods of Treatment

As noted above, the invention is premised on several unique discoveries, and provides the following independent methods that can be practiced according to the present invention, including:

In a first principal embodiment, the invention provides a method of treating nausea and vomiting for a period of five consecutive days in a patient in need thereof, comprising administering to said patient netupitant or a pharmaceutically acceptable salt thereof in an amount which is therapeutically effective to treat nausea and vomiting during the acute and delayed phases, which enters the systemic circulation, crosses the blood brain barrier and occupies at least 70% of NK_1 receptors in the striatum seventy-two hours after said administration.

In a second principal embodiment, the invention provides a combination therapy for treating nausea and vomiting for five consecutive days in a patient in need thereof, comprising:

(i) administering to said patient on day one netupitant or a pharmaceutically acceptable salt thereof, in an amount which is therapeutically effective to treat nausea and vomiting during the acute and delayed phases, which enters the systemic circulation, crosses the blood brain barrier and occupies at least 70% of NK_1 receptors in the striatum seventy-two hours after said administration;

(ii) administering to said patient on day one a therapeutically effective amount of a 5-HT_3 antagonist (preferably palonosetron, more preferably 0.5 mg. of oral palonosetron as palonosetron hydrochloride) effective to treat said nausea and vomiting during the acute and delayed phases;

(iii) administering to said patient on day one a first dose of dexamethasone which is ineffective against nausea and vomiting when administered alone, but effective against nausea and vomiting when administered in combination with said netupitant and palonosetron, wherein said first dose comprises from 50 to 70% of a minimum effective dose when administered alone; and

(iv) if the patient is undergoing highly emetogenic chemotherapy, administering to said patient, on days two, three and four, a second dose of dexamethasone which is ineffective against nausea and vomiting when administered alone, but effective against nausea and vomiting when administered in combination with said netupitant, wherein said second dose comprises from 40 to 60% of a minimum effective dose when administered alone on days two, three and four.

Various sub-embodiments are envisaged for these principal embodiments. For example, the netupitant can be administered as a free base or a pharmaceutically acceptable salt thereof, but is preferably administered as the free base. In addition, the netupitant is preferably administered in an amount ranging from about 50 to about 500 mg., from about 200 to about 400 mg., and preferably about 300 mg., based on the weight of the free base. A preferred route of administration for the netupitant is oral. In terms of binding to NK_1 receptors, the netupitant preferably binds to at least 80 or even 85% of NK_1 receptors in the striatum seventy-two hours after administration. As of ninety six hours after administration, the netupitant preferably binds less than 70, 60, 50 or even 40% of said NK_1 receptors.

The methods of the present invention are all effective at treating or preventing nausea and vomiting induced by numerous events, including chemotherapy induced nausea and vomiting ("CINV"), from moderately or highly emetogenic chemotherapy, radiation therapy induced nausea and vomiting ("RINV"), and post-operative nausea and vomiting ("PONV"). The method is preferably performed shortly before the emesis inducing event (i.e. no more than 1 or 2 hours before the event). The methods may be used to treat nausea and vomiting during the acute phase of emesis, or during the delayed phase.

The drugs specified by the individual embodiments may be administered by any suitable dosing regimen, as is well known in the art, but in a preferred embodiment the netupitant, 5-HT_3 antagonist and steroid are administered orally. A preferred oral dose of palonosetron ranges from about 0.075 to about 1.0 mg, or from about 0.25 to about 0.75 mg, but is preferably about 0.5 mg. A preferred oral dose of netupitant ranges from about 50 to 500 mg, or from about 200 to about 400 mg, but is preferably about 300 mg. A preferred dose of corticosteroid, preferably dexamethasone, is 12 mg administered orally or via injection on the first day of treatment, and 8 mg administered orally or via injection on the second, third and fourth days after said treatment.

It will be further understood that the netupitant can be administered in prodrug form, in which case the invention will provide a method of treatment by inducing plasma levels of netupitant, and in each case the plasma level of netupitant induced by the prodrug administration will correspond to the level attained by the administration of netupitant or its pharmaceutically acceptable salt, in the doses and routes of administration described herein.

Pharmaceutical Compositions

Various pharmaceutical compositions can be developed that make use of the combinations described herein. The composition can be administered by any appropriate route, for example, orally, parenterally, or intravenously, in liquid or solid form.

Preferred modes of administrations of the active compounds are injectable and/or oral. These compositions will generally include an inert diluent or an edible carrier. They may be enclosed in gelatin capsules (for oral use) or compressed into tablets (for oral or buccal use) or formulated into troches (for buccal use). For these purposes, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition.

Tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a gliding such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring. When the dosage unit form is a capsule, it can contain, in addition to material of the above type, a liquid carrier such as a fatty oil. In addition, dosage unit forms can contain various other materials which modify the physical form of the dosage unit, for example, coatings of sugar, shellac, or other enteric agents.

The compounds can be administered as a component of an elixir, suspension, syrup, wafer, orally disintegrating film, orally disintegrating tablet, chewing gum or the like. A syrup may contain, in addition to the active compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors.

Solutions or suspensions used for injection can include the following components: a sterile diluent such as water for

injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride, mannitol and dextrose. An injectable preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

Combined Oral Dosage Forms

As discussed above, the invention provides versatile combined oral dosage forms of palonosetron and an NK1 antagonist that can be readily modified depending on the therapeutic objective, and that do not present issues of stability and degradation. In a preferred embodiment, the invention provides a capsule for oral administration made from a hard outer shell that houses one or more NK1 antagonist tablets and one or more palonosetron soft-gel capsules. The finished capsule and the tablet(s) and soft-gel capsule(s) housed within the capsule shell are all preferably formulated as immediate release dosage forms. Netupitant and casopitant, and their pharmaceutically acceptable salts, are particularly preferred NK_1 antagonists for the combined oral dosage forms of this invention.

While the NK1 antagonist is preferably formulated in a solid tablet, it will be understood that it can be formulated in any solid form that is suitable for oral administration including, for example, a tablet or capsule (hard or soft-gel). In a preferred embodiment, the NK1 antagonist is formulated in a tablet. The number of NK1 antagonist units contained within the combined dosage form can be, for example, from 1 to 10, 1 to 5, or 1 to 3. The netupitant units within the combined dosage form can provide anywhere from 50 to 500 mg of netupitant on an aggregate basis, preferably from 100 to 350 mg. Each netupitant unit preferably comprises from 50 to 200 mg of netupitant, more preferably 100 to 150 mg of netupitant, and most preferably 100 or 150 mg of netupitant.

The palonosetron can also be formulated in any solid form that is suitable for oral administration, although it is preferably formulated as a soft-gel capsule. Non-limiting examples of suitable palonosetron soft-gel capsules are provided in PCT publication WO 2008/049552, the contents of which are hereby incorporated by reference. The number of palonosetron units within the combined dosage from can be, for example, from 1 to 5, from 1 to 3 or just 1. Each of the palonosetron units within the combined dosage form can provide anywhere from 0.01 to 5.0 mg palonosetron, preferably from 0.1 to 1.0 mg palonosetron on an aggregate basis. Each palonosetron unit will preferably comprise from 0.1 to 1.0 mg of palonosetron, most preferably about 0.25, 0.5, 0.75 or 1.0 mg of palonosetron.

FIG. 1 illustrates an exemplary embodiment of a combined oral dosage form of palonosetron and netupitant. The dosage form 10 comprises a two piece hard outer shell that includes a body 20 and a cap 22. The dosage form 10 contains one palonosetron soft-gel capsule 30 (preferably containing 0.5 mg of palonosetron) and three netupitant tablets 40 (each preferably containing 100 mg of netupitant).

Hard Outer Shell

The hard outer shell of the present invention can be made of any pharmaceutically acceptable material that dissolves in gastric fluids. Preferred materials for the hard outer shell include, for example, gelatin, cellulose, starch, or hydroxypropyl methylcellulose (HPMC). In a particular embodiment of the invention, the hard outer shell has a maximum oxygen permeability. Preferably, the oxygen permeability is less about 1.0×10^{-3}, 5.0×10^{-4}, 1.0×10^{-4}, 5.0×10^{-5}, or even 2.0×10^{-5} ml·cm/(cm^2·24 hr. atm).

The hard outer shell can be a continuous structure. Alternatively, the hard outer shell can be a two-piece hard capsule.

Soft-Gel Capsule

The soft-gel capsule used for the palonosetron preferably comprises a soft outer shell and a liquid inner fill composition comprising palonosetron hydrochloride. Non-limiting examples of suitable palonosetron soft-gel capsules are provided in PCT publication WO 2008/049552, the contents of which are hereby incorporated by reference.

The soft outer shell of the soft-gel capsule can contain any type of material that dissolves in gastric fluids. Preferred materials for the soft outer shell include, for example, gelatin, cellulose, starch, or hydroxypropyl methylcellulose (HPMC). The soft-gel capsule can further comprise shell excipients such as glycerin, sorbitol, and colorants/opacifers such as titanium dioxide. The soft-gel capsule can further include solvents such as purified water. In particular embodiments of the invention, the outer shell has a maximum oxygen permeability, preferably of no more than 1.0×10^{-3}, 5.0×10^{-4}, 1.0×10^{-4}, 5.0×10^{-5}, or even 2.0×10^{-5} ml·cm/(cm^2·24 hr. atm). Suitable soft-gel capsules include the 1.5-oval gelatine capsule shell manufactured by Catalent Pharma Solutions.

The liquid fill is preferably composed predominantly of one or more lipophilic components in an amount of from 50 wt. % to 99 wt. %, preferably from 75 wt. % to 98 wt. %. Preferred lipophilic components include, for example, mono- and di-glycerides of fatty acids, especially including the mono- and di-glycerides of capryl/capric acid. The liquid fill may also contain glycerin, preferably in an amount of from 1 to 15 wt. %, more preferably from 2 to 10 wt. %. In one preferred embodiment, both the shell and the inner fill composition comprise glycerin. In another preferred embodiment, the liquid fill comprises about 0.25, 0.50, 0.75 mg., or more of palonosetron as palonosetron hydrochloride.

The fill composition may comprise various means to facilitate the transition of palonosetron from the dosage form to the gastrointestinal fluids of the GI tract, so that the palonosetron may be more readily absorbed into the bloodstream. For example, the liquid fill composition may contain a surfactant, optimally in an amount of from 0.1 wt. % to 6 wt. %, from 0.5 wt. % to 5 wt. %, or from 1.0 wt. % to 3.0 wt. %. The liquid fill composition preferably comprises greater than 0.1, 0.5, or 1.0 wt. % of surfactant, and less than 10, 8, 5, 4, or even 4 wt. % of surfactant. A particularly preferred surfactant is polyglyceryl oleate.

Alternatively or in addition, the transitioning means for a liquid filled capsule may comprise water that forms a single phase or microemulsion with the other liquid ingredients in the excipient base. The liquid fill composition preferably comprises from 0.05 wt. % to 30 wt. % water, from 1 wt. % to 20 wt. % water, or from 2 wt. % to 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.

The active agent, which is preferably palonosetron hydrochloride, is preferably present in the fill composition in an amount ranging from 0.01 to 10.0 wt. %, from 0.05 to 5.0 wt. %, or from 0.1 wt. % to 2.0 wt. %. Alternatively, particularly stable formulations have been found where the concentration of palonosetron exceeds 0.3%, preferably at a concentration no greater than 1 wt. %.

Tablet

The tablets of the present invention can include from 20 to 95 wt. % of NK1 antagonist (preferably netupitant), and preferably comprises from 60 to 80 wt. % of netupitant. In addition, the tablets can contain diluents, disintegrants, sur-

factants, binders, glidants, and/or lubricants. In a particular embodiment, the tablet comprises from 5 to 25 wt. % of microcrystalline cellulose. The microcrystalline cellulose can function as a diluent and disintegrant, and preferably comprises 15 wt. % of the tablet. Another suitable disintegrant is sodium croscaramellose, which can be present in the tablet in an amount of from 1 to 5 wt. %, preferably 2 wt. %.

A suitable binder for use in the tablet is polyvinylpyrrolidone, which can be present in the tablet in an amount from 1 to 10 wt. % of the tablet, and preferably 5 wt. %. A suitable glidant for use in the tablet is colloidal silicon dioxide, which can be present in the tablet in an amount of 2 wt. %. Suitable lubricants for use in the tablet include sodium stearyl fumarate and magnesium stearate, which can be present in the tablet in an amount of 0.7 wt. % and 0.35 wt. %, respectively.

Application of the Combined Oral Dosage Forms

The invention further provides a method of treating emesis comprising orally administering to a patient suffering from emesis, or at risk for suffering emesis, a dosage form of the present invention. In still further embodiments, the invention provides methods of treating emesis by administering one or more of the dosage forms described herein. The dosage form is preferably administered shortly before the emesis inducing event (i.e. no more than 2 hours before the event). The emesis may be acute phase emesis (i.e. emesis experienced within about 24 hours of an emesis inducing event), or delayed emesis (i.e. emesis experienced after the acute phase, but within seven, six, five or four days of an emesis inducing event). The emesis may constitute chemotherapy induced nausea and vomiting ("CINV"), from moderately or highly emetogenic chemotherapy, radiation therapy induced nausea and vomiting ("RINV"), or post-operative nausea and vomiting ("PONV").

EXAMPLES

The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how the compounds claimed herein are made and evaluated, and are intended to be purely exemplary of the invention and are not intended to limit the scope of what the inventors regard as their invention. Efforts have been made to ensure accuracy with respect to numbers (e.g., amounts, temperature, etc.) but some errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, temperature is in ° C. or is at room temperature, and pressure is at or near atmospheric.

Example 1

Preparation of Oral Dosage Form

In a preferred embodiment the combination is administered in a capsule oral dosage form, wherein the capsule houses one or more soft-gel capsules for the palonosetron and one or more hard tablets for the netupitant. Table 1 below describes a representative formulation for a soft-gel capsule containing 0.5 mg of palonosetron, suitable for inclusion in such a hard outer shell.

TABLE 1

REPRESENTATIVE SOFT-GEL FORMULATION

Ingredient	Approximate Amount (mg/Capsule)	Function
Fill Solution		
Palonosetron HCl	0.56[1]	Active
Mono- and di-glycerides of Capryl/ Capric Acid (Capmul MCM)	62.19	Solvent vehicle
Glycerin, anhydrous, USP/Ph Eur	3.37	Plasticizer
Polyglyceryl oleate (Plurol Oleique CC 497)	0.87	Surfactant
Purified water, USP/Ph Eur	2.94	Co-solvent
Butylated hydroxyanisole (BHA), NF/ Ph Eur	0.07	Antioxidant
Nitrogen	—	
Theoretical fill weight	70.00 mg	
Gelatine Capsule Shell, 1.5-oval (Catalent Pharma Solutions)[2]		
Gelatine (type 195), NF/Ph Eur	—	Shell
Sorbitol Special/Glycerin Blend 50/50	—	Plasticizer
Titanium dioxide, USP/Ph Eur	—	Colorant/ Opacifier
Purified water, USP/Ph Eur	—	Solvent

[1]Corresponds to 0.50 mg. free base
[2]Quantitative composition of capsule shell is proprietary to Catalent Pharma Solutions

Table 2 below describes a representative formulation for a tablet containing 100 mg. of netupitant, suitable for inclusion in a hard shell.

TABLE 2

REPRESENTATIVE TABLET FORMULATION

Ingredient	Approximate Amount (mg/Tablet)	Function
Netupitant, milled	100	Active
Microcrystalline cellulose pH 101	20.5	Diluent and disintegrant
Sucrose Lauric Acid Esters	10.0	Surfactant
Polyvinilpyrrolidone K30	7.0	Binder
Sodium croscaramellose	3.0	Disintegrant
Colloidal Silicon Dioxide	3.0	Glidant
Sodium Stearyl Fumarate	1.0	Lubricant
Magnesium Stearate	0.5	Lubricant
Total weight	145 mg	

Example 2

Pharmacokinetics of Combined Dosage Form

Objective

The effects of palonosetron on the pharmacokinetics (PK) of netupitant and the effects of netupitant on the PK of palonosetron were examined in healthy volunteers.

Methods

A randomized, open, 3-way crossover study was conducted. Each subject participated in 3 treatment periods, each lasting approximately 12 days (Day −1 to Day 11). The treatment periods were separated by wash-out periods of no less than 14 days (between Day 1 of any 2 consecutive treatment periods).

The following treatments were investigated:

Treatment A: oral netupitant 450 mg. administered as single dose of three 150 mg. capsules.

Treatment B: oral palonosetron 0.75 mg. and oral netupitant 450 mg. administered simultaneously as three capsules of 150 mg. netupitant followed by 1 capsule of 0.75 mg. palonosetron.

Treatment C: oral palonosetron 0.75 mg. administered as single dose as one 0.75 mg. capsule.

Doses were administered under fasting conditions. Subjects fasted over-night for approximately 10 hours. Water, however, was permitted up to 1 hour pre-dose. Food intake was permitted 4 hours post-dose, and water was allowed ad libitum 1 hour post-dose.

Doses were administered with the subject in an upright position. The subjects remained in an upright position for 4 hours post-dose. The capsules were swallowed whole with 250 mL of room-temperature tap water. Repeated PK blood sampling (for netupitant and/or palonosetron) was performed.

Results

The primary PK variables assessed for netupitant and palonosetron were the maximum plasma concentration observed (C_{max}), the area under the plasma concentration versus time curve from time zero to the last quantifiable sampling time point (t) (AUC_{0-t}), and the area under the plasma concentration versus time curve from time zero to infinity (AUC_{0-inf}). The secondary PK variables assessed were the terminal elimination half-life ($t_{1/2,z}$), and the time at which the maximum plasma concentration was observed (t_{max}). Results are depicted in below Tables 3 and 4, as well as FIGS. **2** and **3**.

TABLE 3

Summary of Netupitant Pharmacokinetic Parameters

Parameter	Netupitant 450 mg	Palonosetron 0.75 mg + Netupitant 450 mg
AUC_{0-t} [h * µg/L]	22808 (7270)	22775 (10064)
AUC_{0-inf} [h * µg/L]	25927 (10156)	26241 (13219)
C_{max} [µg/L]	650.2 (257.8)	659.7 (325.7)
t_{max} (h)	4.50 (3.00; 24.00)	4.50 (3.00; 23.95)
$t_{1/2,z}$ (h)	71.81 (37.10; 261.61)	78.31 (50.17; 196.13)

Mean and SD are shown, except for t_{max} and $t_{1/2}$, where median and range are shown.

As can be seen in Table 4 below, palonosetron shows a better pharmacokinetic profile when combined with Netupitant as opposed to administered as a single dose of palonosetron, for example, the greater AUC, the larger C_{max}, the shorter t_{max}, (the median t_{max} was 0.5 hour shorter after administration of palonosetron in combination with netupitant), and the longer $t_{1/2,z}$.

TABLE 4

Summary of Palonosetron Pharmacokinetic Parameters

Parameter	Palonosetron 0.75 mg	Palonosetron 0.75 mg + Netupitant 450 mg
AUC_{0-t} [h * µg/L]	67415 (19554)	74230 (24866)
AUC_{0-inf} [h * µg/L]	70813 (20415)	77254 (25402)
C_{max} [µg/L]	1638.4 (415.5)	1863.1 (487.1)
t_{max} (h)	5.02 (4.00; 8.00)	4.50 (3.00; 6.02)
$t_{1/2,z}$ (h)	34.73 (19.61; 70.46)	36.91 (20.23; 56.08)

Mean and SD are shown, except for t_{max} and $t_{1/2}$, where median and range are shown.

Example 3

Netupitant+Dexamethasone Drug Interaction Study

The effect of netupitant on orally administered dexamethasone pharmacokinetics was evaluated in this study. This was a randomized, open, 3-period crossover study utilizing an incomplete Latin Square design where subjects were given dexamethasone alone, or oral Netupitant 100 mg., 300 mg. or 450 mg. each given with dexamethasone. Netupitant was given orally on Day 1 only. The dexamethasone regimen for each treatment was 20 mg. orally Day 1, followed by 8 mg. orally every 12 hours from Day 2 through Day 4. Nineteen subjects (12 male and 7 female) completed the study (i.e., all 3 treatment periods).

Mean plasma concentrations of dexamethasone were higher when dexamethasone was co-administered with netupitant (FIG. **4**). The increase appeared to be dependant on the netupitant exposure.

The AUC_{0-24} (Day 1) of dexamethasone increased 1.5, 1.7 and 1.8-fold with co-administration of 100, 300 and 450 mg. netupitant, respectively. The AUC_{24-36} (Day 2) of dexamethasone increased 2.1, 2.4 and 2.6-fold and AUC_{84-108} and AUC_{84-inf} (Day 4) increased 1.7, 2.4 and 2.7-fold, with co-administration of 100, 300 and 450 mg. netupitant, respectively. Dexamethasone C_{max} on Day 1 was only slightly affected by co-administration of netupitant (1.1-fold increase during co-administration with 100 and 300 mg. netupitant, respectively, and 1.2-fold increase during co-administration with 450 mg. netupitant). C_{max} on Day 2 and Day 4 was increased approximately 1.7-fold in subjects administered netupitant. Dexamethasone C_{min} on Days 2-4 was increased approximately 2.8, 4.3 and 4.6-fold with co-administration of 100, 300 and 450 mg. netupitant, respectively. This clearly shows that the co-administration of netupitant and dexamethasone enhances the bioavailability of dexamethasone and provides a better therapeutic window of dexamethasone.

Example 4

Netupitant Pet Receptor Occupancy Study

This was a randomized, open-label, positron emission tomography (PET) study using 11C-GR205171 as tracer in 6 healthy male volunteers (2 per dose level) receiving single doses of netupitant (100, 300 or 450 mg) to investigate the degree of occupancy of NK_1 receptors in human brain, and to determine the relationship between plasma concentration of netupitant and NK_1 receptor occupancy (RO).

The anticipated high NK_1-RO (90% or higher) close to the expected C_{max} (6 hours post dose) was reached for striatum, occipital cortex, frontal cortex and anterior cingulate in 3 of 6 subjects of whom 1 received 300 mg. and 2 received 450 mg. of netupitant as a single oral dose.

All doses showed a relatively long duration of blockade of NK_1 receptors and the decline over time was dose dependent. In the 100 mg. dose group, 4 of 6 regions still had a mean NK_1-RO over 70% at 96 hours post dose. In the highest dose group (450 mg), 5 of 6 regions had a mean NK_1-RO of 80% or higher at 96 hours post dose. A comparison of the results for the dose groups (100 mg., 300 mg. and 450 mg) showed a consistent but small increase in NK_1-RO, with increasing netupitant dose. (FIG. **5**)

Example 5

Clinical Efficacy Study

A phase 2 trial evaluated three single doses of netupitant combined with palonosetron and dexamethasone compared to palonosetron alone and dexamethasone to obtain dose ranging information for netupitant used with oral palonosetron in the CINV patient population.

The objective of the study was to compare the efficacy and safety of three single oral doses of netupitant combined with oral palonosetron and given with dexamethasone, versus oral palonosetron-alone given with dexamethasone (without netupitant) for the prevention of highly emetogenic chemotherapy (HEC)-induced nausea and vomiting. The FDA-approved oral aprepitant regimen given with IV ondansetron and dexamethasone was included in the study as an active comparator for exploratory purposes. The FDA-approved oral palonosetron 0.5 mg. dose was used in each applicable treatment group in this study.

This was a multicenter, randomized, double-blind, double-dummy, parallel group, stratified study. Eligible patients were randomized (stratified by gender) to one of the following treatment groups:

Group 1—0.5 mg. oral palonosetron on Day 1 (with an oral dexamethasone standard regimen: 20 mg. on Day 1 and 8 mg. BID from Day 2 through Day 4)

Group 2—100 mg. oral netupitant plus 0.5 mg. oral palonosetron on Day 1 (with an oral dexamethasone adjusted regimen*: 12 mg. on Day 1 and 8 mg. daily from Day 2 through Day 4)

Group 3—200 mg. oral netupitant plus 0.5 mg. oral palonosetron on Day 1 (with an oral dexamethasone adjusted regimen*: 12 mg. on Day 1 and 8 mg. daily from Day 2 to Day 4)

Group 4—300 mg. oral netupitant plus 0.5 mg. oral palonosetron on Day 1 (with dexamethasone adjusted regimen*: 12 mg. on Day 1 and 8 mg. daily from Day 2 to Day 4)

Group 5—125 mg. oral aprepitant plus IV ondansetron 32 mg. (both on Day 1) then 80 mg. oral aprepitant on Day 2 and Day 3, (all with an oral dexamethasone adjusted regimen: 12 mg. on Day 1 and 8 mg. daily from Day 2 through Day 4)

In addition, a Group 6 was added to the analysis for comparative purposes, based on the results reported by Grunberg et al., Support Cancer Care (2009) 17:589-594:

Group 6--285 mg. oral aprepitant plus 20 mg. oral dexamethasone plus 0.2 mg. palonosetron i.v. (all on Day 1) then 80 mg. oral aprepitant

The primary efficacy endpoint was the complete response rate (defined as no emetic episodes, no rescue medication) within 120 hours after the start of the highly emetogenic chemotherapy administration. Secondary efficacy endpoints were:

Complete response for the 0-24 hour interval (acute phase); and for the 25-120 hour interval (delayed phase);

Complete protection (defined as no emesis, no rescue therapy, no significant nausea); Total control (defined as no emesis, no rescue therapy and no nausea); No nausea (maximum VAS<5 mm); No significant nausea (maximumVAS<25 mm); No rescue medication; No emesis. These endpoints were evaluated for the 0-120 hour interval (overall), acute and delayed phase.

Time to first emetic episode, Time to first rescue medication, Time to treatment failure (based on time to the first emetic episode or time to the first rescue medication, whichever occurs first);

Severity of nausea for the overall, acute and delayed phase;

• Patient global satisfaction with anti-emetic therapy by means of VAS for each 24 hour interval.

Complete response rates are summarized in Table 5. The percent of patients with complete response over 0-120 hours after start of cisplatin administration was 76.5% in the palonosetron alone group and 87.4%, 87.6%, and 89.6% in the netupitant 100 mg., 200 mg., and 300 mg. groups, respectively. Differences from palonosetron-alone were greater than 10% (10.9% to 13.2%). All doses of netupitant were statistically superior to palonosetron alone (p-value=0.004 for the netupitant 300 mg. combination group).

TABLE 5

COMPLETE RESPONSE RATE FOR THE OVERALL, ACUTE AND DELAYED PHASE: MFAS Population

Efficacy endpoint	Palo alone (n = 136)	Palo + Netu 100 mg (n = 135)	Palo + Netu 200 mg (n = 137)	Palo + Netu 300 mg (n = 135)	Aprepitant Regimen (N = 134)
CR, Overall Phase, 0-120 h					
Percent of Patients	76.5	87.4	87.6	89.6	86.6
Difference from Palo alone (%)		10.9	11.1	13.2	10.1
p-value (*)		0.018	0.017	0.004	0.027
CR, Acute Phase, -24 h					
Percent of Patients	89.7	93.3	92.7	98.5	94.8
Difference from Palo alone (%)		3.6	3.0	8.8	5.1
p-value (*)		0.278	0.383	0.007	0.114
CR, Delayed Phase, 25-120 h					
Percent of Patients	80.1	90.4	91.2	90.4	88.8
Difference from Palo alone (%)		10.2	11.1	10.2	8.7
p-value (*)		0.018	0.010	0.018	0.043

(*) p-value from logistic regression analysis, aprepitant p-value from post-hoc logistic regression analysis.

Table 6 summarizes results for main secondary endpoints. In the overall phase, 76.5% of patients in the palonosetron-alone group did not experience emesis, while 87.4, 87.6, and 91.1% of patients did not experience emesis in the netupitant 100 mg., 200 mg. and 300 mg. combination groups, respectively ($p<0.05$ for all doses).

TABLE 6

SUMMARY OF SECONDARY EFFICACY RESULTS: PERCENT OF PATIENTS, MFAS POPULATION

Efficacy endpoint	Palo alone (n = 136)	Palo + Netu 100 mg (n = 135)	Palo + Netu 200 mg (n = 137)	Palo + Netu 300 mg (n = 135)	Aprepitant Regimen (N = 134)	Palo + Aprep 285 mg (N = 41)**
No Emesis						
Overall	76.5	87.4*	87.6*	91.1*	87.3	
Acute	89.7	93.3	92.7	98.5*	94.8	
Delayed	80.1	90.4*	91.2*	91.9*	89.6*	
No Rescue						
Overall	95.6	97.8	100	98.5	97.8	
Acute	97.8	99.3	100	100	100	
Delayed	97.1	97.8	100	98.5	97.8	
No Nausea						
Overall	50.7	54.8	62.0	61.5	58.2	32
Acute	75.0	72.6	77.4	80.0	77.6	59
Delayed	53.7	59.3	65.0	68.1*	60.4	41
No Significant Nausea						
Overall	79.4	80.0	86.1	89.6*	85.8	56
Acute	93.4	94.1	94.2	98.5*	94.0	79
Delayed	80.9	81.5	89.8*	90.4*	88.1	59
Total Control						
Overall	50.0	54.8	61.3	59.3	56.0	
Acute	71.3	71.9	76.6	80.0	74.6	
Delayed	52.2	59.3	65.0*	65.9*	58.2	
Complete Protection						
Overall	69.9	76.3	80.3*	83.0*	78.4	51
Acute	87.5	89.6	88.3	97.0*	89.6	76
Delayed	73.5	80.0	87.6*	84.4*	82.1	66

*p-value, 0.05 compared with palonosetron-alone; aprepitant comparisons p-values calculated by post-hoc analysis

**As reported by Grunberg et al., Support Cancer Care (2009) 17: 589-594

Example 7

Comparative Results of Aprepitant Dosing Regimen

The following Table 8 reports the results observed for an aprepitant dosing regimen, as described in the FDA approved prescribing information for aprepitant, which demonstrates, among other things, that aprepitant has no meaningful effect on nausea. Table 7 reports the dosing regimen:

TABLE 7

Treatment Regimen	Day 1	Day 2 to 4
Aprepitant	Aprepitant 125 mg PO	Aprepitant 80 mg PO Daily
	Dexamethasone	(Days 2 and 3 only)
	12 mg PO Ondansetron	Dexamethasone 8 mg PO Daily
	32 mg I.V.	(morning)

TABLE 8

Percent of Patients Receiving Highly Emetogenic Chemotherapy Responding by Treatment Group and Phase for Study 1 - Cycle 1

ENDPOINTS	Aprepitant Regimen (N = 260)† %	Standard Therapy (N = 261)† %	p-Value
PRIMARY ENDPOINT			
Complete Response			
Overall‡	73	52	<0.001
OTHER PRESPECIFIED ENDPOINTS			
Complete Response			
Acute phase[1]	89	78	<0.001
Delayed Phase[2]	75	56	<0.001
Complete Protection			
Overall	63	49	0.001
Acute phase	85	75	NS*
Delayed phase	66	52	<0.001
No Emesis			
Overall	78	55	<0.001
Acute phase	90	79	0.001
Delayed phase	81	59	<0.001

TABLE 8-continued

Percent of Patients Receiving Highly Emetogenic Chemotherapy Responding by Treatment Group and Phase for Study 1 - Cycle 1

ENDPOINTS	Aprepitant Regimen (N = 260)† %	Standard Therapy (N = 261)† %	p-Value
No Nausea			
Overall	48	44	NS**
Delayed phase	51	48	NS**
No Significant Nausea			
Overall	73	66	NS**
Delayed phase	75	69	NS**

†N: Number of patients (older than 18 years of age) who received cisplatin, study drug, and had at least one post-treatment efficacy evaluation.
‡Overall: 0 to 120 hours post-cisplatin treatment.
[1]Acute phase: 0 to 24 hours post-cisplatin treatment.
[2]Delayed phase: 25 to 120 hours post-cisplatin treatment.
*Not statistically significant when adjusted for multiple comparisons.

Throughout this application, various publications are referenced. The disclosures of these publications in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art to which this invention pertains. It will be apparent to those skilled in the art that various modifications and variations can be made in the present invention without departing from the scope or spirit of the invention. Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims.

The invention claimed is:

1. A method of treating chemotherapy induced nausea and vomiting (CINV) comprising administering to a subject receiving chemotherapy a regimen of palonosetron, netupitant and dexamethasone.

2. A method of treating chemotherapy induced nausea and vomiting (CINV) in a subject receiving chemotherapy comprising administering to a subject receiving chemotherapy a regimen of netupitant and a sub-therapeutic dose of dexamethasone.

3. The method of claim **2**, wherein the sub-therapeutic dose of dexamethasone comprises from about 50 to 70% of a minimum effective dose when administered alone against CINV.

4. A method of treating chemotherapy induced nausea and vomiting (CINV) comprising inducing in a subject receiving chemotherapy blood levels of palonosetron and netupitant effective to treat said CINV.

5. The method of claim **1**, wherein the chemotherapy comprises moderately or highly emetogenic chemotherapy.

6. The method of claim **1**, wherein said chemotherapy comprises carboplatin.

7. The method of claim **1**, wherein the netupitant and palonosetron are administered no more than one hour prior to administration of the chemotherapy.

8. The method of claim **1**, wherein when said chemotherapy is highly emetic chemotherapy, the chemotherapy is selected from the group consisting of carmustine, cisplatin, cyclophosphamide≥1500 mg/m^2, dacarbazine, dactinomycin, mechlorethamine, streptozotocin and combinations thereof.

9. The method of claim **1**, wherein when said chemotherapy is moderately emetic chemotherapy, the chemotherapy is selected from the group consisting of carboplatin, cyclophosphamide<1500 mg/m^2, cytarabine>1 mg/m^2, daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, oxaliplatin and combinations thereof.

10. The method of claim **1**, wherein said chemotherapy is selected from the group consisting of carboplatin, cyclophosphamide, cytarabine>1 mg/m^2, daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, carmustine, cisplatin, dacarbazine, dactinomycin, mechlorethamine, streptozotocin, oxaliplatin and combinations thereof.

11. The method of claim **2**, wherein when said chemotherapy is highly emetic chemotherapy, the chemotherapy is selected from the group consisting of carmustine, cisplatin, cyclophosphamide≥1500 mg/m^2, dacarbazine, dactinomycin, mechlorethamine, streptozotocin and combinations thereof.

12. The method of claim **2**, wherein when said chemotherapy is moderately emetic chemotherapy, the chemotherapy is selected from the group consisting of carboplatin, cyclophosphamide<1500 mg/m^2, cytarabine>1 mg/m^2, daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, oxaliplatin and combinations thereof.

13. The method of claim **2**, wherein said chemotherapy is selected from the group consisting of carboplatin, cyclophosphamide, cytarabine>1 mg/m^2, daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, carmustine, cisplatin, dacarbazine, dactinomycin, mechlorethamine, streptozotocin, oxaliplatin and combinations thereof.

14. The method of claim **4**, wherein when said chemotherapy is highly emetic chemotherapy, the chemotherapy is selected from the group consisting of carmustine, cisplatin, cyclophosphamide≥1500 mg/m^2, dacarbazine, dactinomycin, mechlorethamine, streptozotocin and combinations thereof.

15. The method of claim **4**, wherein when said chemotherapy is moderately emetic chemotherapy, the chemotherapy is selected from the group consisting of carboplatin, cyclophosphamide<1500 mg/m^2, cytarabine>1 mg/m^2, daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, oxaliplatin and combinations thereof.

16. The method of claim **4**, wherein said chemotherapy is selected from the group consisting of carboplatin, cyclophosphamide, cytarabine>1 mg/m^2, daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, carmustine, cisplatin, dacarbazine, dactinomycin, mechlorethamine, streptozotocin, oxaliplatin and combinations thereof.

17. The method of claim **1**, wherein said treatment of CINV is defined as no emetic episodes and no use of rescue medication following said chemotherapy.

18. The method of claim **1**, wherein:

a) said regimen comprises a single administration of netupitant or pharmaceutically acceptable salt thereof and a single administration of palonosetron or pharmaceutically acceptable salt thereof;

b) said netupitant or pharmaceutically acceptable salt thereof and said palonosetron or pharmaceutically acceptable salt thereof are administered concomitantly and prior to said chemotherapy, without administering a second dose of either for at least five days after said cheniotherapy; and

c) said regimen is effective to treat said CINV for a five day period after said chemotherapy.

19. The method of claim **1**, wherein:

a) said treatment of CINV is defined as no emetic episodes and no use of rescue medication following said chemotherapy;

b) said regimen comprises a single administration of netupitant or pharmaceutically acceptable salt thereof and a

single administration of palonosetron or pharmaceutically acceptable salt thereof;

c) said netupitant or pharmaceutically acceptable salt thereof and said palonosetron or pharmaceutically acceptable salt thereof are administered concomitantly and prior to said chemotherapy, without administering a second dose of either for at least five days after said chemotherapy; and

d) said regimen is effective to treat said CINV for a five day period after said chemotherapy.

20. The method of claim **19**, wherein:

a) said netupitant is administered orally as the free base in a dose of from about 200 mg to about 400 mg; and

b) said palonosetron is administered orally as palonosetron hydrochloride in a dose of from about 0.25 mg to about 0.75 mg based on the weight of the free base.

21. The method of claim **19**, wherein:

a) said netupitant is administered orally as the free base in a dose of about 300 mg;

b) said palonosetron is administered orally as palonosetron hydrochloride in a dose of about 0.50 mg based on the weight of the free base; and

c) said netupitant and palonosetron are administered as a single unit dosage form less than 2 hours prior to said chemotherapy.

22. The method of claim **19**, wherein:

a) said chemotherapy comprises moderately emetogenic chemotherapy;

b) said netupitant is administered orally as the free base in a dose of about 300 mg;

c) said palonosetron is administered orally as palonosetron hydrochloride in a dose of about 0.50 mg based on the weight of the free base;

d) said netupitant and palonosetron are administered as a combination unit dosage form less than 2 hours prior to said chemotherapy; and

e) said dexamethasone is administered in a dose of about 12 mg, in a dosage form independent of said combination unit dosage form, less than 2 hours prior to said chemotherapy.

23. The method of claim **19**, wherein:

a) said chemotherapy comprises highly emetogenic chemotherapy;

b) said netupitant is administered orally as the free base in a dose of about 300 mg;

c) said palonosetron is administered orally as palonosetron hydrochloride in a dose of about 0.50 mg based on the weight of the free base;

d) said netupitant and palonosetron are administered as a combination unit dosage form less than 2 hours prior to said chemotherapy;

e) said dexamethasone is administered in a dose of about 12 mg, in a dosage form independent of said combination unit dosage form, less than 2 hours prior to said chemotherapy; and

f) said dexamethasone is further administered in a dose of about 8 mg on days 2, 3 and 4 following said chemotherapy.

24. The method of claim **19**, wherein said netupitant occupies at least 70% of said patient's striatum NK1 receptors ninety-six hours after said administration.

25. The method of claim **19**, wherein:

a) said chemotherapy is highly emetogenic chemotherapy; and

b) said netupitant is effective to treat said CINV during the acute and delayed phases of said CINV.

26. The method of claim **19**, wherein:

a) said chemotherapy is highly emetogenic chemotherapy; and

b) said regimen is effective to prevent nausea or reduce the severity of nausea in said patient during the acute and delayed phases of said CINV.

27. The method of claim **19**, wherein:

a) said chemotherapy is moderately emetogenic chemotherapy; and

b) said regimen is effective to prevent nausea or reduce the severity of nausea in said patient during the acute and delayed phases of said CINV.

28. The method of claim **19**, wherein (3S)-3-[(3aS)-1-oxo-2,3,3a,4,5,6-hexahydro-1H-benzo[de]isoquinoline-2-yl]-1-azoniabicyclo[2.2.2]octan-1-olate is substantially absent from said palonosetron.

29. The method of claim **19**, wherein said netupitant occupies at least 70% of said patient's striatum NK1 receptors ninety-six hours after said administration.

30. The method of claim **19**, wherein said chemotherapy comprises cisplatin.

31. The method of claim **19**, wherein said chemotherapy comprises carboplatin, cisplatin, oxaliplatin, or doxorubicin.

32. The method of claim **19**, wherein said chemotherapy comprises cyclophosphamide.

33. The method of claim **21**, wherein:

a) said chemotherapy is highly emetogenic chemotherapy; and

b) said netupitant is effective to treat said CINV during the acute and delayed phases of said CINV.

34. The method of claim **21**, wherein:

a) said chemotherapy is highly emetogenic chemotherapy; and

b) said regimen is effective to prevent nausea or reduce the severity of nausea in said patient during the acute and delayed phases of said CINV.

35. The method of claim **21**, wherein:

a) said chemotherapy is moderately emetogenic chemotherapy; and

b) said regimen is effective to prevent nausea or reduce the severity of nausea in said patient during the acute and delayed phases of said CINV.

36. The method of claim **21**, wherein said netupitant occupies at least 70% of said patient's striatum NK1 receptors ninety-six hours after said administration.

37. The method of claim **21**, wherein said chemotherapy comprises cisplatin.

38. The method of claim **21**, wherein said chemotherapy comprises carboplatin, cisplatin, oxaliplatin, or doxorubicin.

39. The method of claim **21**, wherein said chemotherapy comprises cyclophosphamide.

40. The method of claim **2**, wherein said treatment of CINV is defined as no emetic episodes and no use of rescue medication following said chemotherapy.

41. The method of claim **2**, wherein:

a) said regimen comprises a single administration of netupitant or pharmaceutically acceptable salt thereof, without administering a second dose for at least five days after said chemotherapy;

b) said chemotherapy comprises moderately emetogenic or highly emetogenic chemotherapy;

c) if said chemotherapy comprises moderately emetogenic chemotherapy, said regimen comprises a single administration of dexamethasone without administering a second dose for at least five days after said chemotherapy;

d) if said chemotherapy comprises highly emetogenic chemotherapy, said regimen comprises administering a first

dose of dexamethasone on day one and a second dose of dexamethasone on two, three and four after said chemotherapy;

e) said netupitant or pharmaceutically acceptable salt thereof and said first dose of dexamethasone are administered prior to said chemotherapy;

f) said regimen is effective to treat said CINV for a five day period after said chemotherapy.

42. The method of claim **2**, wherein:

a) said treatment of CINV is defined as no emetic episodes and no use of rescue medication following said chemotherapy;

b) said regimen comprises a single administration of netupitant or pharmaceutically acceptable salt thereof, without administering a second dose for at least five days after said chemotherapy;

c) said chemotherapy comprises moderately emetogenic or highly emetogenic chemotherapy;

d) if said chemotherapy comprises moderately emetogenic chemotherapy, said regimen comprises a single administration of dexamethasone without administering a second dose for at least five days after said chemotherapy;

e) if said chemotherapy comprises highly emetogenic chemotherapy, said regimen comprises administering a first dose of dexamethasone on day one and a second dose of dexamethasone on two, three and four after said chemotherapy;

f) said netupitant or pharmaceutically acceptable salt thereof and said first dose of dexamethasone are administered prior to said chemotherapy;

g) said regimen is effective to treat said CINV for a five day period after said chemotherapy.

43. The method of claim **35**, wherein:

a) said chemotherapy comprises moderately emetogenic chemotherapy;

b) said netupitant is administered orally as the free base in a dose of about 300 mg less than 2 hours prior to said chemotherapy; and

c) said single administration of dexamethasone comprises about 12 mg, in a dosage form independent of said netupitant less than 2 hours prior to said chemotherapy.

44. The method of claim **35**, wherein:

a) said chemotherapy comprises highly emetogenic chemotherapy;

b) said netupitant is administered orally as the free base in a dose of about 300 mg less than 2 hours prior to said chemotherapy;

c) said first dose of dexamethasone comprises about 12 mg, in a dosage form independent of said netupitant, administered less than 2 hours prior to said chemotherapy; and

d) said second dose comprises about 8 mg of dexamethasone administered on days 2, 3 and 4 following said chemotherapy.

45. The method of claim **35**, wherein said netupitant occupies at least 70% of said patient's striatum NK1 receptors ninety-six hours after said administration.

46. The method of claim **35**, wherein said netupitant is effective to treat said CINV during the acute and delayed phases of said CINV.

47. The method of claim **35**, wherein said regimen is effective to prevent nausea in said patient following the administration of said chemotherapy.

48. The method of claim **35**, wherein said regimen is effective to reduce the severity of nausea in said patient following the administration of said chemotherapy.

49. The method of claim **35**, wherein said chemotherapy comprises cisplatin.

50. The method of claim **35**, wherein said chemotherapy comprises carboplatin, cisplatin, oxaliplatin, or doxorubicin.

51. The method of claim **35**, wherein said chemotherapy comprises cyclophosphamide.

52. The method of claim **4**, wherein said treatment of CINV is defined as no emetic episodes and no use of rescue medication following said chemotherapy.

53. The method of claim **4**, wherein:

a) said blood levels are induced by an intravenous antiemetic regimen administered prior to said chemotherapy; and

b) said regimen is effective to treat said CINV for a five day period after said chemotherapy.

54. The method of claim **4**, 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 antiemetic regimen administered prior to said chemotherapy; and

c) said regimen is effective to treat said CINV for a five day period after said chemotherapy.

55. The method of claim **54**, wherein said netupitant occupies at least 70% of said patient's striatum NK1 receptors ninety-six hours after said administration.

56. The method of claim **54**, 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.

57. The method of claim **54**, 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.

58. The method of claim **54**, 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.

59. The method of claim **54**, 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.

60. The method of claim **54**, wherein said chemotherapy comprises cisplatin.

61. The method of claim **54**, wherein said chemotherapy comprises carboplatin, cisplatin, oxaliplatin, or doxorubicin.

62. The method of claim **54**, wherein said chemotherapy comprises cyclophosphamide.

* * * * *

APPENDIX E

APPENDIX E

SUMMARY OF SIGNIFICANT EVENTS DURING REGULATORY REVIEW PERIOD

Date *yymmdd*	**Action Type**	**Application No.**	**Description**
150625	Initial IND	IND 115191	Initial IND - submission of NEPA-15-18 protocol, IB, TOSO and 1572 of 1st investigator
150709	Amendment	IND 115191	Response to FDA Request (07.08.15) and submission of Informed Consent Form
150714	Amendment	IND 115191	Response to FDA Request (07.09.15) and submission of claim for categorical exclusion from Environmental Assessment
150717	Amendment	IND 115191	Response to FDA Request (07.15.15) on stopping criteria
150720	Amendment	IND 115191	Response to FDA Request (07.17.15) on CMC (glucose solution CoA and endotoxin tests)
150722	Amendment	IND 115191	Response to FDA Request (07.20.15) and commitment to have a DSMB
150723	Amendment	IND 115191	Response to FDA Request (07.22.15) on pH of the solution of IV NEPA FDC
150724	Amendment	IND 115191	Response to FDA Request (07.23.15) with proposal of new pH and acceptance limits
150803	Amendment	IND 115191	Response to FDA Request (07.28.15) with submission of updated section 3.2.P.2.6
150806	Amendment	IND 115191	Submission of FDA Form 3674
151019	Amendment	IND 115191	Submission of protocol amendment 1 (DSMB inclusion)
151028	Amendment	IND 115191	Submission of protocol amendment 2 (minor) and DSMB charter requested by FDA on 07.20.15
151209	Amendment	IND 115191	Submission of PSP with partial waiver and deferral request
151214	Amendment	IND 115191	Submission of 1572 and CV for new investigators for NEPA-15-18
160118	Amendment	IND 115191	Submission of protocol amendment 3D (local for Germany) and 1572/CV for new investigators
160125	Amendment	IND 115191	Submission of updated stability data in 3.2.P.8.1 and 3.2.P.8.3
160218	Amendment	IND 115191	Submission of 1572 and CV for new investigators for NEPA-15-18
160321	Amendment	IND 115191	Submission of 1572 and CV for new investigators for NEPA-15-18
160324	Amendment	IND 115191	Submission of revised iPSP and request for deferral according to FDA request of 03.08.16
160324	Amendment	IND 115191	Submission of a request for a Type C meeting (ISE, ISS, dataset)
160420	Amendment	IND 115191	Submission of protocol amendment 3 (time windows) and 1572/CV for new investigators and corresponding Protocol amendment 3.1D (local for Germany)
160425	Amendment	IND 115191	Submission of revised iPSP and request for deferral according to FDA request of 04.12.16
160602	Amendment	IND 115191	Submission of agreed iPSP and request for deferral according to FDA request of 06.01.16

160603	Amendment	IND 115191	Submission of protocol NEPA-15-19, 1572 for investigator, labels and TOSO
160829	Amendment	IND 115191	Request of a guidance on proprietary name Akynzeo
160909	Amendment	IND 115191	Submission of IND annual report as DSUR (reporting period 26 Jul 2015 - 25 Jul 2016)
160915	Amendment	IND 115191	Request for a pre-NDA meeting
160927	Amendment	IND 115191	Submission of 1572 and CV for new investigators for NEPA-15-18
161012	Amendment	IND 115191	Request for proprietary name review, according to request received on 09.29.16
161027	Amendment	IND 115191	Submision of background package for pre-NDA meeting scheduled for 11.30.16
161129	Amendment	IND 115191	Submission of sponsor replies to preliminary written responses received by FDA
161222	Amendment	IND 115191	Submission of assessment of fosnetupitant potential to prolong QT interval and request for waiver for a QT/QTc study
170712	Amendment	IND 115191	Submission of protocol NEPA-17-05 with TOSO
170921	Amendment	IND 115191	Submission of IND annual report as DSUR (reporting period 26 Jul 2016 - 25 Jul 2017)
180111	Amendment	IND 115191	Submission of protocol NEPA-17-05 amendment 1 (addition of new CRO) and new TOSO
180111	Amendment	IND 115191	Submission of protocol NEPA-17-05 amendment 2 (new title and change of design)
180111	Amendment	IND 115191	Submission of protocol NEPA-17-05 amendment 3 and investigational drug labeling
180226	Amendment	IND 115191	Submission of 1572 and CV for new investigators for NEPA-17-05
180406	Amendment	IND 115191	Submission of 1572 and CV for new investigators for NEPA-17-05
180508	Amendment	IND 115191	Submission of 1572 and CV for new investigators for NEPA-17-05
170420	Original Application	NDA 210493	Original NDA submission
170426	Amendment	NDA 210493	Response to FDA Request (04.25.17) and submission of a clean copy of proposed PI and PPI
170530	Amendment	NDA 210493	Response to FDA-requested clarification (05.23.17) of PNET-12-23 datasets
170601	Amendment	NDA 210493	Submission of FDA-requested (05.17.17) additional information and amended labeling according PLLR
170608	Amendment	NDA 210493	Sponsor's response to FDA Information Request (06.07.17) for SAS macro programs for studies PALO-15-17 and NEPA-15-18
170706	Amendment	NDA 210493	Sponsor's response to FDA Information Request (06.29.17) for CMC information: microbiology test on finished products and palonosetron specifications
170712	Product Correspondence	NDA 210493	Communication on US Authorized Representative Vacation
170717	Amendment	NDA 210493	Response to FDA Clinical Information Request (07.12.17) on blood creatinine increase in study NEPA-15-18

170719	Amendment	NDA 210493	Response to Clinical Information Request (07.11.17) on efficacy results in study NEPA-15-18
170719	Amendment	NDA 210493	Submission of amended labeling according to requests provided in Filing letter of 06.28.17
170727	Amendment	NDA 210493	Notification of response to FDA Request (07.10.17) for Method Verification Materials and submission of methods
170816	Amendment	NDA 210493	Response to FDA Clinical Information Request (08.01.17) on NEPA-15-18 efficacy results
170816	Amendment	NDA 210493	Reply to FDA's Clinical Pharmacology Information Request (08.08.17) for PNET-12-23 BE data
170831	Amendment	NDA 210493	Response to FDA Clinical Information Request (08.23.17) on NEPA-15-18 efficacy results
170831	Amendment	NDA 210493	Response to FDA Clinical Information Request (08.28.17) on PALO-15-17 cardiac safety
170906	Amendment	NDA 210493	Submission of 4-month safety update
170913	Amendment	NDA 210493	Response to FDA Clin. Pharm. Information Request (09.11.17, item 4) on PNET-12-23 dataset
170926	Amendment	NDA 210493	Response to FDA Clinical information Request (09.19.17) on efficacy of NEPA-15-18
170926	Amendment	NDA 210493	Response to FDA Clinical information Request (09.21.17) on patients data of NEPA-15-18
170927	Amendment	NDA 210493	Response to FDA Information Request (09.11.17, item 1-3) on PNET-16-29 additional data
171005	Amendment	NDA 210493	CMC amendment (module 32S update following HAS modification of the DMF agreed with FDA)
171012	Amendment	NDA 210493	Response to Mid-Cycle Significant Review Issue
171012	Amendment	NDA 210493	Response to clinical Information request (10.03.17) on liver safety in NEPA-15-18
171013	Amendment	NDA 210493	Response to CMC Information request (10.10.17)
171020	Amendment	NDA 210493	Response to Clinical Information request (10.13.17) addressing potential drug interactions between fosnetupitant and palonosetron, and comparing cross study pk information
171102	Amendment	NDA 210493	Response to Clinical Information request (10.27.17) asking for additional analyses on non-responder subgroups in NEPA-15-18
171103	Amendment	NDA 210493	Response to CMC Information request (10.25.17) asking for clarification on manufacturing process and controls
171109	Amendment	NDA 210493	Response to Clinical Pharmacology Information request (11.03.17) asking for clarification on palonosetron transporter inhibition, time dependent inhibition of fosnetupitant and PNET-12-23 dataset
171128	Amendment	NDA 210493	Response to CMC/labeling Information request (11.13.17) asking for amended carton and label
171212	Amendment	NDA 210493	Response to nonclinical Information request (12.05.17) asking for characterization on extractables
171214	Amendment	NDA 210493	Response to CMC/labeling Information request (12.11.17) asking for amended carton and label
180108	Amendment	NDA 210493	Response to revision to proposed labeling request (14.12.17) asking for amended PI and PPI

180110	Amendment	NDA 210493	Agreement to proposed Post Marketing Requirements and Commitments (sent by FDA on 22.12.17)
180312	Amendment	NDA 210493	Revised Prescribing Information (PI) and Container Label (FDA request on Feb 28, 2018)
180405	Amendment	NDA 210493	Response to Clinical Information request (March 27, 2018) on safety and adverse events in studies PALO-15-17 an NEPA-15-18
180412	Amendment	NDA 210493	Revised Prescribing Information (PI) (FDA request on Apr 10, 2018)
180417	Amendment	NDA 210493	Revised Prescribing Information (PI) and patient information (PPI) (FDA request on Apr 16, 2018)
180419	Amendment	NDA 210493	Revised Prescribing Information (PI) and patient information (PPI) (FDA request on Apr 18, 2018)
180419	Approval	NDA 210493	FDA Approval Letter Sent

Document code: WFEE

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Application Number	14/069927
Filing Date	11/01/2013
First Named Inventor	Fabio Trento
Title	COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING
Art Unit	1619
Examiner Name	Webb, Walter E.
Attorney Docket Number	

SIGNATURE of Applicant or Patent Practitioner

Signature	/Clark G. Sullivan/	Date (Optional)	2018-06-11
Name	Clark G. Sullivan	Registration Number	36942
Title (if Applicant is a juristic entity)			
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Helsinn Healthcare SA

☐ Inventor or Joint Inventor (title not required below)

☐ Legal Representative of a Deceased or Legally Incapacitated Inventor (title not required below)

☑ Assignee or Person to Whom the Inventor is Under an Obligation to Assign (provide signer's title if applicant is a juristic entity)

☐ Person Who Otherwise Shows Sufficient Proprietary Interest (e.g., a petition under 37 CFR 1.46(b)(2) was granted in the application or is concurrently being filed with this document) (provide signer's title if applicant is a juristic entity)

SIGNATURE of Applicant for Patent

The undersigned (whose title is supplied below) is authorized to act on behalf of the applicant (e.g., where the applicant is a juristic entity).

Signature		Date (Optional)	
Name	Matteo Missaglia		
Title	GENERAL COUNSEL & CHIEF LEGAL OFFICER		

NOTE: Signature - This form must be signed by the applicant in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. If more than one applicant, use multiple forms.

☐ Total of forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

PTO/AIA/96 (08-12)
Approved for use through 01/31/2013. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

STATEMENT UNDER 37 CFR 3.73(c)

Applicant/Patent Owner: HELSINN HEALTHCARE SA

Application No./Patent No.: 9186357 Filed/Issue Date: 11/17/2015

Titled: COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING

HELSINN HEALTHCARE SA, a corporation

(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that, for the patent application/patent identified above, it is (choose **one** of options 1, 2, 3 or 4 below):

1. ☑ The assignee of the entire right, title, and interest.

2. ☐ An assignee of less than the entire right, title, and interest (check applicable box):

   ☐ The extent (by percentage) of its ownership interest is _____%. Additional Statement(s) by the owners holding the balance of the interest must be submitted to account for 100% of the ownership interest.

   ☐ There are unspecified percentages of ownership. The other parties, including inventors, who together own the entire right, title and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

3. ☐ The assignee of an undivided interest in the entirety (a complete assignment from one of the joint inventors was made). The other parties, including inventors, who together own the entire right, title, and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

4. ☐ The recipient, via a court proceeding or the like (*e.g.*, bankruptcy, probate), of an undivided interest in the entirety (a complete transfer of ownership interest was made). The certified document(s) showing the transfer is attached.

The interest identified in option 1, 2 or 3 above (not option 4) is evidenced by either (choose **one** of options A or B below):

A. ☑ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel 034886, Frame 0944, or for which a copy thereof is attached.

B. ☐ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

   1. From: _____ To: _____

      The document was recorded in the United States Patent and Trademark Office at

      Reel _____, Frame _____, or for which a copy thereof is attached.

   2. From: _____ To: _____

      The document was recorded in the United States Patent and Trademark Office at

      Reel _____, Frame _____, or for which a copy thereof is attached.

This collection of information is required by 37 CFR 3.73(b). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

PTO/AIA/96 (08-12)
Approved for use through 01/31/2013. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

STATEMENT UNDER 37 CFR 3.73(c)

3. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

4. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

5. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

6. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

☐ As required by 37 CFR 3.73(c)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (i.e., a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

/Clark G. Sullivan/	2018-06-11
Signature	Date
Clark G. Sullivan	36942
Printed or Typed Name	Title or Registration Number

Electronic Acknowledgement Receipt

EFS ID:	32853820
Application Number:	14069927
International Application Number:	
Confirmation Number:	3207
Title of Invention:	COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING
First Named Inventor/Applicant Name:	Fabio TRENTO
Customer Number:	6980
Filer:	Clark G. Sullivan
Filer Authorized By:	
Attorney Docket Number:	244168.000015US4
Receipt Date:	13-JUN-2018
Filing Date:	01-NOV-2013
Time Stamp:	15:50:41
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		14069927_POA.pdf	372465 7c4703e167789d3fd754433217e745873c1eee5f	yes	4

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Power of Attorney	1	2
	Assignee showing of ownership per 37 CFR 3.73	3	4
Warnings:			
Information:			
	Total Files Size (in bytes):	372465	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.
National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.
New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
14/069,927	11/01/2013	Fabio TRENTO	

CONFIRMATION NO. 3207

POA ACCEPTANCE LETTER

140619
Sullivan IP Solutions, LLC
PO Box 2252
New York, NY 10163

OC000000100343461

Date Mailed: 06/18/2018

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 06/13/2018.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/trwoodson/

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
14/069,927	11/01/2013	Fabio TRENTO	244168.000015US4

CONFIRMATION NO. 3207

POWER OF ATTORNEY NOTICE

6980
TROUTMAN SANDERS LLP
600 PEACHTREE ST NE STE 3000
ATLANTA, GA 30308-2219

OC000000100343453

Date Mailed: 06/18/2018

NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 06/13/2018.

- The Power of Attorney to you in this application has been revoked by the assignee who has intervened as provided by 37 CFR 3.71. Future correspondence will be mailed to the new address of record(37 CFR 1.33).

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/trwoodson/

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22314-1450
www.uspto.gov

Clark G. Sullivan
Sullivan IP Solutions
P.O. Box 2252
New York, NY 10163

In Re: Patent Term Extension
Application for
U.S. Patent No. 9,186,357
Filed: June 12, 2018

FEB 14 2019

REQUIREMENT FOR INFORMATION PURSUANT TO 37 C.F.R. 1.750

An application for extension of the patent term of U.S. Patent No. 9,186,357 under 35 U.S.C. § 156 was filed in the United States Patent and Trademark Office on June 12, 2018. The application (PTE application) was filed by Helsinn Healthcare SA, the patent owner of record. Extension is sought based upon the premarket review under § 505 of the Federal Food, Drug, and Cosmetic Act (FFDCA) of Akynzeo® for Injection (fosnetupitant & palonosetron), which was approved for commercial use and sale by the Food and Drug Administration (FDA) on April 19, 2018. An extension of 519 days is requested.

35 U.S.C. 156 states:

> (a) The term of a patent which claims a product, a method of using a product, or a method of manufacturing a product shall be extended in accordance with this section from the original expiration date of the patent, which shall include any patent term adjustment granted under section 154(b) if . . .
>
> > (4) the product has been subject to a regulatory review period before its commercial marketing or use;. . . .
>
> (f) For purposes of this section:
> > (1) The term "product" means:
> > > (A) A drug product . . .
> >
> > (2) The term "drug product" means the active ingredient of—
> > > (A) a new drug, antibiotic drug, . . . as those terms are used in the Federal Food, Drug, and Cosmetic Act . . . including any salt or ester of the active ingredient, as a single entity or in combination with another active ingredient.

Accordingly, one of the requirements for a patent to be eligible for extension, pursuant to the provisions of 35 U.S.C. 156, is that the patent must claim the approved product, a method of using the approved product or a method of manufacturing the approved product. See 35 U.S.C. 156(a). 35 U.S.C. 156(f)(2)(A) further clarifies that in the case of a drug product, the patent must claim an active ingredient (including any salt or ester) of the approved product, or a method of using or manufacturing an active ingredient (including any salt or ester) of the approved product. Here, the patent claims are method of use claims, but it appears that the claims do not recite a method of using an active ingredient (including any salt or ester) of the approved drug product.

Each of Helsinn's patent claims 4, 14, 16, 52, 53, 55, 56, 58, 60, 61 and 63 encompasses a method of using netupitant. Claim 4 is representative. It recites, "[a] method of treating chemotherapy induced nausea and vomiting (CINV) comprising inducing in a subject receiving chemotherapy blood levels of palonosetron and netupitant effective to treat said CINV." The specification describes the administration of netupitant with palonosetron or netupitant with dexamethasone. The approved product, on the other hand, is Akynzeo® for Injection, which is a combination of two active ingredients, known by the common names fosnetupitant and palonosetron. Fosnetupitant and netupitant are not the same. Importantly, netupitant is not a salt or ester of fosnetupitant. Instead, fosnetupitant is an ester of netupitant, specifically a phosphate ester of netupitant.

Thus, Helsinn's patent does not claim fosnetupitant or palonosetron, or a method of using or manufacturing fosnetupitant or palonosetron. Nor does Helsinn's patent claim a salt or ester of fosnetupitant or palonosetron, or a method of using or manufacturing a salt or ester of fosnetupitant or palonosetron. Instead, Helsinn's patent claims a method of using netupitant, which is neither an active ingredient of Akynzeo® for Injection or a salt or ester of an active ingredient of Akynzeo® for Injection.

Caselaw confirms that netupitant is not an active ingredient of Akynzeo® for njection and that Helsinn's patent does not claim Akynzeo® for Injection. "[A]n 'ingredient' must be present in the drug product when administered." *Glaxo Operations UK, Ltd. v. Quigg*, 706 F. Supp. 1224, 1227-28, 10 USPQ2d 1100,1103 (E.D. Va. 1989), *aff'd* 894 F. 2d 392, 13 USPQ2d 1628 (Fed. Cir 1990). Netupitant is not present in the approved product when administered. Further, "[a] patent which claims a metabolite of an approved drug does not claim the approved drug." *Hoechst-Roussel Pharmaceuticals Inc. v. Lehman*, 109 F.3d 756, 759, 42 USPQ2d 1220, 1223 (Fed. Cir. 1997). Here, claim 4 is directed to a method of using the metabolite (netupitant) of the approved product (fosnetupitant).

Applicant has **TWO MONTHS** from the date of this letter in order to file a response which addresses the USPTO's initial finding that the patent does not claim a method of using the approved product. Extensions of time under 37 CFR 1.136 are available. Failure to respond will result in the application for patent term extension being dismissed.

Any correspondence from applicant with respect to this matter should be submitted via the USPTO's EFS Web system and should be addressed as follows:

By mail: Commissioner for Patents
Mail Stop Hatch-Waxman PTE
P.O. Box 1450
Alexandria, VA 22313-1450

Telephone inquiries related to this notice should be directed to the undersigned at (571) 272-7755.

Mary C. Till
Senior Legal Advisor
Office of Patent Legal Administration
Office of the Deputy Commissioner
for Patent Examination Policy

cc: FDA, CDER, Office of Regulatory Policy
10903 New Hampshire Avenue,
Bldg. 51 Room 6250
Silver Spring MD 20993-0002

Attention: Beverly Friedman

RE: AKYNZEO® for Injection
(fosnetupitant & palonosetron)
Docket No.: FDA-2019-E-

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re: U.S. Patent No. 9,186,357 B1

Issued: November 17, 2015

To: Fabio TRENTO et al.

For: COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING

Commissioner for Patents
Mail Stop Hatch-Waxman PTE
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE TO REQUIREMENT FOR INFORMATION

Dear Commissioner:

This letter is submitted in response to the Office's February 14, 2019, Requirement for Information Pursuant to 37 C.F.R. 1.750.

BACKGROUND

Fosnetupitant is a prodrug of netupitant, and one of the active ingredients in Akynzeo® for injection (Akynzeo® i.v.). Netupitant was originally developed as an oral capsule and approved by the United States Food and Drug Administration ("FDA") on October 10, 2014, for the treatment of chemotherapy induced nausea and vomiting ("CINV"). However, netupitant cannot be injected due to its limited solubility. To overcome this limitation, Applicant developed fosnetupitant, a prodrug of netupitant, and secured FDA approval for fosnetupitant as Akynzeo® i.v. on April 19, 2018.

When Akynzeo® i.v. is injected, the fosnetupitant is converted to netupitant by metabolic hydrolysis, and thereafter converted to three predominant metabolites. As explained in the FDA-approved prescribing information for Akynzeo® i.v. (previously supplied):

Metabolism

> Fosnetupitant is converted in vivo to netupitant by metabolic hydrolysis. In patients receiving AKYNZEO intravenously, netupitant exposure was 17-fold fosnetupitant exposure, as determined by their AUC_{inf} ratio. Netupitant metabolites M1, M2 and M3 were generated from the released netupitant. In patients, metabolite M1, M2 and M3 exposures were 32%, 21% and 28% of netupitant exposure. The median t_{max} for M1, M2, and M3 were 12, 2 and 12 hours, respectively.

The patent at issue in this Request for Patent Term Extension ("PTE"), U.S. Patent No. 9,186,357 B1 ("the '357 patent"), discloses and claims the use of netupitant and its prodrugs in combination with palonosetron to treat CINV. The patent describes the combined administration of palonosetron and netupitant or a prodrug of netupitant. A specific disclosure of prodrugs is found in column 10, lines 22-29 of the '357 patent, wherein it is stated:

> It will be further understood that the netupitant can be administered in prodrug form, in which case the invention will provide a method of treatment by inducing plasma levels of netupitant, and in each case the plasma level of netupitant induced by the prodrug administration will correspond to the level attained by the administration of netupitant or its pharmaceutically acceptable salt, in the doses and routes of administration described herein.

The use of prodrugs of netupitant to treat CINV, by inducing sufficient blood levels of netupitant, is captured in claim 4, wherein it is stated:

> 4. A method of treating chemotherapy induced nausea and vomiting (CINV) comprising inducing in a subject receiving chemotherapy blood levels of palonosetron and netupitant effective to treat said CINV.

Claim 4 claims a method of treating CINV by inducing levels of netupitant in the bloodstream effective to treat CINV. This claim covers a method of using Akynzeo® i.v. to treat CINV because Akynzeo® i.v. "induces in a subject receiving chemotherapy blood levels of palonosetron and netupitant effective to treat said CINV." In fact, the claim covers the use of any drug that is capable of inducing blood levels of palonosetron and netupitant that are effective to treat CINV.

DISCUSSION

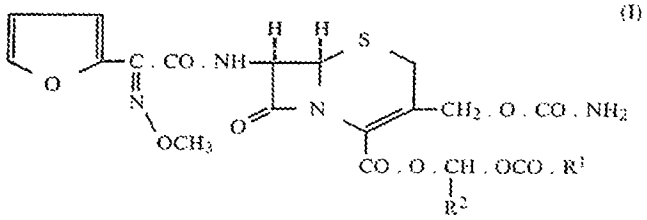
The statute at issue, 35 U.S.C. § 156, states in subsection (a):

> (a) The term of a patent which claims a product, a method of using a product, or a method of manufacturing a product shall be extended in accordance with this section from the original expiration date of the patent … if—
> (1) the term of the patent has not expired before an application is submitted under subsection (d) for its extension;
> (2) the term of the patent has never been extended;
> (3) an application for extension is submitted by the owner of record of the patent … in accordance with the requirements of subsection (d);
> (4) the product has been subject to a regulatory review period before its commercial marketing or use;
> (5) (A) … the permission for the commercial marketing or use of the product … is the first permitted commercial marketing or use of the product under the provision of law under which such regulatory review period occurred …

35 U.S.C. § 156(a). As can be seen, the statute states in compulsory terms that a patent shall be extended if it claims "a product, a method of using a product, or a method of manufacturing a product," and conditions (1)-(5) are satisfied. Because claim 4 of the '357 patent claims a method of using Akynzeo® i.v. for the treatment approved by FDA, and conditions (1)-(5) are unquestionably satisfied, the '357 patent is eligible for a patent term extension under section 156(a).

The Office cites *Glaxo Operations UK v. Quigg*, 706 F. Supp. 1224, 1227-28, 10 USPQ2d 1100, 1103 (E.D. Va. 1989), *aff'd* 894 F.2d 392, 13 USPQ2d 1628 (Fed. Cir. 1990), for the proposition that "an ingredient must be present in the drug product when administered" for a patent to qualify for a PTE, and argues that "[n]etupitant is not present in the drug product when administered" to support its initial denial of Applicant's request, but *Glaxo v. Quigg* actually supports a PTE in this case. In *Glaxo v. Quigg*, FDA had approved Glaxo's Ceftin®, which contained cefuroxime axetil as its active ingredient. The patent at issue, U.S. Patent No. 4,267,320, was a compound patent that claimed cefuroxime axetil in independent claim 1 and dependent claim 4, reproduced below:

1. A cephalosporin antibiotic of the sym form having a formula



(I)

(wherein R^1 is a primary or secondary alkyl group containing 1 to 4 carbon atoms and R^2 is a primary or secondary alkyl group containing 1 to 6 carbon atoms provided that at least one of the groups R^1 and R^2 is methyl).

4. The compound claimed in claim 1 which is 1-acetoxyethyl (6R,7R)-3-carbamoyloxymethyl-7-[(Z)-2-(fur-2-yl)-2-methoxyiminoacetamido]ceph-3-em-4-carboxyylate.

The Commissioner initially refused to extend the term of the patent because, according to the Commissioner, cefuroxime was the active ingredient in Ceftin, not cefuroxime axetil, and FDA had previously approved cefuroxime as the sodium salt. *See* 706 F.2d at 1102 ("The central question then is whether the active ingredient of Ceftin Tablets is the ester cefuroxime axetil or the parent acid cefuroxime.") Essentially, the Commissioner was applying an "active moiety" approach to its PTE determinations, similar to the approach FDA takes when determining whether a molecule qualifies for new chemical entity exclusivity. The district court rejected this active moiety approach, in a decision that was subsequently affirmed by the Federal Circuit. The district court reversed the Commissioner because "[i]t is cefuroxime axetil that is the "active ingredient" in Ceftin Tablets. Cefuroxime itself is not present at all in Ceftin Tablets; it is therefore not an 'ingredient.'" *Id.*

As in *Glaxo v. Quigg*, it is fosnetupitant that is the "active ingredient" in Akynzeo i.v., and it is fosnetupitant (which is a prodrug of netupitant, according to the specification as detailed hereinbefore) that is claimed in claim 4[1]. Claim 4 of the '357 patent is a method of treatment

[1] Claim 4 does not spell out the chemical structure of fosnetupitant, but it claims the use of fosnetupitant to treat CINV inasmuch as the administration of fosnetupitant induces therapeutically effective levels of netupitant in the bloodstream, as recited in claim 4. Claim 4 may describe

claim using fosnetupitant, and Glaxo's claim was a product claim, but Section 156 is not limited to product claims. Under 35 U.S.C. 156(a), any "patent which claims a product, a method of using a product, or a method of manufacturing a product" is eligible for extension if the requirements in subsections (1)-(5) are satisfied. Because claim 4 of the '357 patent claims "a method of using" Akynzeo® i.v., and conditions (1)-(5) are satisfied, the '357 patent is eligible for extension.

The Office cites a second court decision, *Hoechst-Roussel Pharm., Inc. v. Lehman*, 109 F.3d 756, 759 42 USPQ2d 1220, 1223 (Fed. Cir. 1997), for the proposition that "[a] patent which claims a metabolite of an approved drug does not claim the approved drug." According to the Office, claim 4 does not entitle Applicant to a PTE because "claim 4 is directed to a method of using the metabolite (netupitant) of the approved product (fosnetupitant)."

However, claim 4 is not directed to the use of netupitant to treat CINV. Instead, the claim is directed to the use of any compound that induces therapeutically effective levels of netupitant in the bloodstream to treat CINV, thus including prodrugs of netupitant, as described in the specification and, namely, fosnetupitant. Netupitant is recited in the claim, but merely as a downstream effect of the claimed method.

In *Hoechst-Roussel Pharm., Inc. v. Lehman*, in contrast, Warner Lambert Company ("Warner Lambert") had secured an FDA approval for tacrine hydrochloride, and Hoechst Roussel Pharmaceuticals ("Hoechst"), a third party embroiled in patent litigation with Warner Lambert, had filed a request for PTE based on Warner Lambert's approval. However, Hoechst's patent did not claim tacrine hydrochloride, but instead claimed 1-hydroxy-tacrine, a metabolite of tacrine hydrochloride, and a method of using 1-hydroxy tacrine by administering 1-hydroxy tacrine to a patient in need of memory enhancement. The Commissioner denied the request for PTE, and the Federal Circuit affirmed the Commissioner's decision, because "Hoechst has not claimed either the active ingredient that received FDA approval, tacrine hydrochloride, or a method of using that ingredient." *Hoechst* at 759.

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fosnetupitant functionally, based on its ability to induce therapeutically effective levels of netupitant, but this functional description is authorized by cases summarized in MPEP 2173.05(g). *See, e.g., In re Swinehart*, 439 F.2d 210, 212, 169 USPQ 226, 229 (CCPA 1971) (holding that Applicant was entitled to claim a genus of compounds "transparent to infrared rays", even though this was a functional description).

Unlike the patent involved in *Hoechst*, Helsinn has claimed a method of using the ingredient approved by FDA. The '357 patent does not claim a method of using a metabolite of fosnetupitant. The claim refers to netupitant, but only as a compound "induced" by the claimed method. Instead, the claim covers a method of inducing netupitant in the bloodstream, including by administering fosnetupitant, and thus claims a method of using the ingredient approved by FDA, fosnetupitant. Therefore, the '357 patent is eligible for a patent term extension.

CONCLUSION

WHEREFORE, a certificate of correction extending the term of U.S. Patent No. 9,186,357 B1 for a period of 519 days to April 19, 2032, is earnestly solicited.

Respectfully submitted,

By: /Clark G. Sullivan/__
Clark G. Sullivan
Reg. No. 36,942

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Sullivan IP Solutions
PO Box 2252
New York NY 10163
404.483.9360

Customer No. 140619

Electronic Patent Application Fee Transmittal

Application Number:	14069927
Filing Date:	01-Nov-2013
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:	

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 $0 paid	1251	1	200	200
Miscellaneous:				
			Total in USD ($)	**200**

Electronic Acknowledgement Receipt

EFS ID:	35854737
Application Number:	14069927
International Application Number:	
Confirmation Number:	3207
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:	
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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	Miscellaneous Incoming Letter	Response_to_Request_for_Information.pdf	278509 99e6aff90e29a5a2320376648925f4396b220b64	no	6
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30753 ad2e3ff257e30dc27bcea660235472097688 4cd7	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	309262		

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.

AO 120 (Rev. 08/10)

TO:	**Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313–1450**	**REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK**

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the **U.S. District Court for the District of New Jersey** on the following:
____ Trademarks or **X** Patents. (____ the patent action involves 35 U.S.C. § 292.)

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
3:22–cv–04635–ZNQ–LHG	7/19/2022	TRENTON, NJ
PLAINTIFF HELSINN HEALTHCARE S.A.		DEFENDANT GLAND PHARMA LIMITED

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1 US 8,426,450 B1	4/23/2013	Helsinn Healthcare SA
2 US 8,895,586 B2	11/25/2014	Luca Fadini, Peter Manini, Claudio Pietra, Claudio Giuliano, Emanuela Lovati, Roberta Cannella, Alessio Venturini, Valentino J. Stella
3 US 9,186,357 B2	11/17/2015	HELSINN HEALTHCARE SA
4 US 9,403,772 B2	8/2/2016	HELSINN HEALTHCARE SA
5 US 9,908,907 B2	3/6/2018	Helsinn Healthcare SA

In the above––entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ___ Amendment ___ Answer ___ Cross Bill ___ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1		
2		
3		
4		
5		

In the above––entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE
William T. Walsh	s/ Karlee Thorpe	7/19/2022

Copy 1––Upon initiation of action, mail this copy to Director Copy 3––Upon termination of action, mail this copy to Director
Copy 2––Upon filing document adding patent(s), mail this copy to Director Copy 4––Case file copy

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
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August 8, 2024

Mr. Clark G. Sullivan
Sullivan IP Solutions, LLC
P.O. Box 2252
New York, NY 10163

In re: Patent Term Extension
Application for
U.S. Patent No. 9,186,357

NOTICE OF FINAL DETERMINATION – INELIGIBLE

On June 12, 2018, patent owner Helsinn Healthcare SA (Helsinn) filed a patent term extension (PTE) application under 35 U.S.C. 156 for extension of U.S. Patent No. 9,186,357 (the '357 patent). Helsinn seeks 519 days of extension based upon the premarket review under § 505 of the Federal Food, Drug, and Cosmetic Act (FFDCA) of AKYNZEO® for Injection (fosnetupitant chloride hydrochloride and palonosetron hydrochloride). The approved product AKYNZEO® for Injection received approval for commercial use and sale by the Food and Drug Administration (FDA) on April 19, 2018.

In connection with the PTE application, the United States Patent and Trademark Office (USPTO) issued a Requirement for Information Pursuant to 37 CFR 1.750 (the RFI) on February 14, 2019. Helsinn filed a Response to Requirement for Information (the Response) on April 29, 2019, which was timely in view of a one-month extension of time under 37 CFR 1.136.

35 U.S.C. 156 states:

> (a) The term of a patent which claims a product, a method of using a product, or a method of manufacturing a product shall be extended in accordance with this section from the original expiration date of the patent, which shall include any patent term adjustment granted under section 154(b) if . . .
>
> > (4) the product has been subject to a regulatory review period before its commercial marketing or use; . . .
> >
> > (5)(A) except as provided in subparagraph (B) or (C),[1] the permission for the commercial marketing or use of the product after such regulatory review period is the first permitted commercial marketing or use of the product under the provision of law under which such regulatory review period occurred . . .
>
> (f) For purposes of this section:

[1] Subparagraphs (B) and (C) concern recombinant DNA technology and products for animals, respectively, and thus are not relevant to the issue at hand.

> (1) The term "product" means:
> (A) A drug product . . .
> (2) The term "drug product" means the active ingredient of—
> (A) a new drug, antibiotic drug, . . . as those terms are used in the Federal Food, Drug, and Cosmetic Act . . . including any salt or ester of the active ingredient, as a single entity or in combination with another active ingredient.

Consistently, 37 CFR 1.740(a)(9) provides that a PTE application must claim the approved product, or a method of using or manufacturing it:

> A formal application for the extension of patent term must include:
> . . . .
> (9) A statement that the patent claims the approved product, or a method of using or manufacturing the approved product . . .

Thus, in order to be eligible for extension, a patent must claim the approved product, a method of using the approved product or a method of manufacturing the approved product. 35 U.S.C. 156(a) and 37 CFR 1.740(a)(9). In the case of a drug product, the patent must claim an active ingredient (including any salt or ester) of the approved product, or a method of using or manufacturing an active ingredient (including any salt or ester) of the approved product. 35 U.S.C. 156(f)(2)(A). The product must have been subject to a regulatory review period, and the approval obtained must have resulted in the first permitted commercial marketing or use, under the provision of law under which such regulatory review period occurred, of at least one of the active ingredients of the product. *Arnold P'ship v. Dudas*, 362 F.3d 1338, 1341 (Fed. Cir. 2004) ("To extend the term of a patent claiming a composition comprising A and B, either A or B must not have been previously marketed. In other words, at least one of the claimed active ingredients must be new to the marketplace as a drug product.") See also 35 U.S.C. 156(a)(5)(A) and 35 U.S.C. 156(f)(2)(A).

Here, Helsinn asserts at page 6 of the PTE application that claims 4, 14, 16, 52–66, 58, 60, 61 and 62 of the '357 patent claim a method of using the approved product AKYNZEO® for Injection. Helsinn does not assert that the '357 patent claims the approved product or a method of manufacturing it. Furthermore, Helsinn asserts at page 4 of the PTE application that although active ingredient palonosetron had previously been approved under § 505 of the FFDCA, active ingredient fosnetupitant had not. Thus, no issue concerning product or method of manufacturing claims drawn to fosnetupitant chloride hydrochloride arises, nor is there any issue concerning claims to palonosetron hydrochloride. In short, the eligibility of the '357 patent for extension turns on the question of whether it claims a method of using fosnetupitant chloride hydrochloride, or any salt or ester thereof.

In the RFI, the USPTO discussed the statutory requirement for claiming the approved product or a method of using or manufacturing it, and reviewed representative claim 4 which reads as follows:

> **4.** A method of treating chemotherapy induced nausea and vomiting (CINV) comprising inducing in a subject receiving chemotherapy blood levels of palonosetron and netupitant effective to treat said CINV.

We pointed out that the claims of the '357 patent do not recite a method of using an active ingredient (including any salt or ester) of the approved drug product AKYNZEO® for Injection. We recognized that the specification describes the administration of netupitant with palonosetron, or netupitant with dexamethasone. However, we also stressed that fosnetupitant and netupitant are not the same, and that netupitant is neither a salt nor an ester of fosnetupitant. We concluded as follows in the RFI:

> Thus, Helsinn's patent does not claim fosnetupitant or palonosetron, or a method of using or manufacturing fosnetupitant or palonosetron. Nor does Helsinn's patent claim a salt or ester of fosnetupitant or palonosetron, or a method of using or manufacturing a salt or ester of fosnetupitant or palonosetron. Instead, Helsinn's patent claims a method of using netupitant, which is neither an active ingredient of Akynzeo® for Injection or a salt or ester of an active ingredient of Akynzeo® for Injection.

We relied on case law to support our assertion that netupitant is not an active ingredient of AKYNZEO® for Injection. First, "an 'ingredient' must be present in the drug product when administered." *Glaxo Operations UK, Ltd. v. Quigg*, 706 F. Supp. 1224, 1227–28, 10 USPQ2d 1100,1103 (E.D. Va. 1989), aff'd 894 F. 2d 392, 13 USPQ2d 1628 (Fed. Cir 1990). Because netupitant is not present in the approved product when administered, it cannot be considered an active ingredient of AKYNZEO® for Injection. Second, "a patent which claims a metabolite of an approved drug does not claim the approved drug." *Hoechst-Roussel Pharmaceuticals Inc. v. Lehman*, 109 F.3d 756, 759, 42 USPQ2d 1220, 1223 (Fed. Cir. 1997). Here, while claim 4 may be said to encompass a method of using netupitant, netupitant is a metabolite of the approved product (fosnetupitant chloride hydrochloride) and not the approved product itself.

Helsinn's argument in the Response of April 29, 2019 to the RFI can be summarized as follows: Claim 4 covers a method of using fosnetupitant chloride hydrochloride, which is an active ingredient of AKYNZEO® for Injection, because administration of the prodrug fosnetupitant chloride hydrochloride results in the blood levels of netupitant required by claim 4. Helsinn points out at page 2 of the Response that column 10, lines 22–29, of the '357 patent discusses administration of a prodrug in order to attain the blood level of netupitant required by claim 4:

> It will be further understood that the netupitant can be administered in prodrug form, in which case the invention will provide a method of treatment by inducing plasma levels of netupitant, and in each case the plasma level of netupitant induced by the prodrug administration will correspond to the level attained by the administration of netupitant or its pharmaceutically acceptable salt, in the doses and routes of administration described herein.

In footnote 1 beginning on page 4 of the Response, Helsinn admits that claim 4 does not directly claim a method of using fosnetupitant chloride hydrochloride, but nevertheless asserts that such a method is covered using functional language:

> [1] Claim 4 does not spell out the chemical structure of fosnetupitant, but it claims the use of fosnetupitant to treat CINV inasmuch as the administration of fosnetupitant induces therapeutically effective levels of netupitant in the bloodstream, as recited in claim 4. Claim 4 may describe fosnetupitant functionally, based on its ability to induce therapeutically effective levels of netupitant, but this functional description is authorized by cases summarized in MPEP 2173.05(g). *See, e.g., In re Swinehart*, 439 F.2d 210, 212, 169 USPQ 226, 229 (CCPA 1971) (holding that Applicant was entitled to claim a genus of compounds "transparent to infrared rays", even though this was a functional description).

Helsinn is generally correct that functional language in claims is not proscribed. However, Helsinn's reliance on *In re Swinehart* and MPEP 2173.05(g) is misplaced. Seemingly in support of Helsinn's position, the *Swinehart* court states, "By its own literal terms a claim employing such [functional] language covers any and all embodiments which perform the recited function." *Id.* at 213. However, *Swinehart* places a constraint on this conclusion in the immediately following sentence: "Legitimate concern often properly exists, therefore, as to whether the scope of protection defined thereby is warranted by the scope of enablement indicated and provided by the description contained in the specification." *Id.*

The *Swinehart* composition of matter claim upheld by the CCPA used the functional language "transparent to infrared rays" to further limit a claim that was otherwise defined by its physical components. In claim 4 at issue here, the functional language "blood levels of palonosetron and netupitant effective to treat said CINV" stands alone as an objective, and does not further limit the manner in which the claimed "inducing" is to be carried out. Thus, the *Swinehart* facts are distinguishable from the case at hand, and the *Swinehart* conclusion does not apply.

Looking to the specification to ascertain the "scope of protection" defined by the claim as counseled by *Swinehart* supports the conclusion that the method covered by claim 4 is not a method of using fosnetupitant chloride hydrochloride or a salt or ester thereof. Helsinn points to the discussion of administration of prodrugs of netupitant at column 10, lines 22–29, of the '357 patent (quoted above) to bolster its assertion that claim 4 covers administration of fosnetupitant chloride hydrochloride. Fosnetupitant chloride hydrochloride may in fact be a prodrug of netupitant. However, the '357 patent does not teach that fosnetupitant chloride hydrochloride, or any other form of fosnetupitant, is a prodrug of netupitant. It does not appear that there is any mention of fosnetupitant in the '357 patent at all. Furthermore, there is no evidence of record in the prosecution history of the '357 patent to indicate that a person of ordinary skill in the art would understand that a reference to "prodrugs" of netupitant would necessarily encompass fosnetupitant chloride hydrochloride. Finally, although the '357 patent states at column 3, lines 19–21, that "[m]ethods of synthesizing and formulating netupitant and its prodrugs are described in U.S. Pat. Nos. 6,297,375, 6,719,996 and 6,593,472 to Hoffmann La Roche," those patents also do not appear to refer to fosnetupitant as a prodrug of netupitant, or at all.

The only drug taught in the '357 patent that could satisfy the functional limitation of "blood levels of . . . netupitant effective to treat said CINV" is netupitant, or a salt thereof. Therefore, claim 4 does not encompass a method of using fosnetupitant chloride hydrochloride or a salt or ester thereof. The "scope of protection" provided by claim 4 can only possibly extend to netupitant and its salts. As explained in the RFI, netupitant is not the same as the active ingredient fosnetupitant chloride hydrochloride, and netupitant is also not a salt or ester of fosnetupitant chloride hydrochloride. At best, claim 4 encompasses a method of using netupitant. Because netupitant is not present in the approved product when administered, as explained above and on page 2 of the RFI, the '357 patent is not eligible for PTE.

The USPTO has determined that U.S. Patent No. 9,186,357 is **NOT** eligible for patent term extension under 35 U.S.C. 156 based upon the regulatory review period of AKYNZEO® for Injection (fosnetupitant chloride hydrochloride and palonosetron hydrochloride) because the '357 patent does not claim a method of using fosnetupitant chloride hydrochloride, or any salt or ester thereof.

Helsinn may file a single request for reconsideration of this FINAL DETERMINATION OF INELIGIBILITY within TWO MONTHS of the mailing date of this letter. The period for response may be extended pursuant to 37 CFR 1.136. See 37 CFR 1.750. A failure to respond to this letter will result in the application papers being placed into the patent file with no further action taken on the application for patent term extension.

Applicant has **TWO MONTHS** from the date of this letter to file a response which addresses the USPTO's determination that the patent does not claim a method of using the approved product. Extensions of time under 37 CFR 1.136 are available. Failure to respond will result in the application for patent term extension being dismissed.

Any correspondence from the PTE applicant with respect to this matter should be submitted via the USPTO patent electronic filing system using the appropriate document description.

Inquiries related to this determination should be directed to the undersigned at 571-272-7754 or kathleen.fonda@uspto.gov.

/Kathleen Kahler Fonda/
Kathleen Kahler Fonda
Senior Legal Advisor
Office of Patent Legal Administration

cc: FDA, CDER, Office of Regulatory Policy
10903 New Hampshire Avenue
Bldg. 51, Room 6250
Silver Spring, MD 20993-0002

Attention: Beverly Friedman

re: AKYNZEO® for Injection
(fosnetupitant chloride
hydrochloride and palonosetron
hydrochloride)