

IN THE UNITED STATES DISTRICT COURT  
FOR THE EASTERN DISTRICT OF PENNSYLVANIA

HELSINN HEALTHCARE S.A.  
Via Pian Scairolo, 9, CH-6912  
Lugano-Pazzallo, Switzerland

and

ROCHE PALO ALTO LLC,  
One DNA Way, South  
San Francisco, California 94080-4990

Plaintiffs,

v.

QILU PHARMACEUTICAL CO., LTD.  
Hightech Industry Park Xinda Street Dongshou,  
Jinan, 250101 China

and

QILU PHARMA, INC.,  
101 Lindenwood Drive, Suite 225  
Malvern, PA 19355

Defendants.

Civil Action No. \_\_\_\_\_

**COMPLAINT FOR  
PATENT INFRINGEMENT**

**(Filed Electronically)**

Plaintiffs Helsinn Healthcare S.A. (“Helsinn”) and Roche Palo Alto LLC (“Roche”) (collectively, “Plaintiffs”), for their Complaint against Qilu Pharmaceutical Co., Ltd. and its United States subsidiary Qilu Pharma, Inc. (collectively, “Qilu” or “Defendants”), hereby allege as follows:

**THE PARTIES**

1. Helsinn is a Swiss corporation having its principal place of business at Via Pian Scairolo, 9, CH-6912 Lugano-Pazzallo, Switzerland.

2. Roche is a company, organized and existing under the laws of the State of Delaware, having a principal place of business at One DNA Way, South San Francisco, California 94080-4990.

3. Upon information and belief, Qilu Pharmaceutical Co., Ltd. is a Chinese company located at Hightech Industry Park Xinda Street Dongshou, Jinan, 250101 China, having a United States subsidiary, Qilu Pharma, Inc.

4. Upon information and belief, Qilu Pharma, Inc. is a corporation organized and existing under the laws of the State of Pennsylvania, with its principal place of business at 101 Lindenwood Drive, Suite 225, Malvern, PA 19355.

5. Upon information and belief, Qilu develops, manufactures, imports, markets, distributes, and/or sells generic pharmaceutical versions of branded products for sale and use throughout the United States, including in the State of Pennsylvania and this Judicial District.

#### **NATURE OF THE ACTION**

6. This is a civil action concerning the infringement of United States Patent No. 7,947,724 (“the ’724 patent”), United States Patent No. 8,729,094 (“the ’094 patent”), United States Patent No. 9,066,980 (“the ’980 patent”), and United States Patent No. 9,173,942 (“the ’942 patent”) (collectively, the “patents-in-suit”). This action arises under the patent laws of the United States, 35 U.S.C. §§ 100 *et seq.*, as well as the Declaratory Judgment Act, 28 U.S.C. §§ 2201-02.

#### **JURISDICTION AND VENUE**

7. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a) and the Declaratory Judgment Act, 28 U.S.C. §§ 2201-02.

8. This Court may declare the rights and other legal relations of the parties pursuant to 28 U.S.C. §§ 2201-02 because this case is an actual controversy within the Court's jurisdiction.

9. Venue is proper in this Court as to Qilu pursuant to 28 U.S.C. §§ 1391(b), (c), and/or (d), and 1400(b).

10. This Court has personal jurisdiction over Qilu because, *inter alia*, it has committed, or aided, abetted, contributed to, or participated in the commission of, acts of patent infringement, including acts in the State of Pennsylvania, that have led to foreseeable harm and injury to Plaintiffs in the State of Pennsylvania. This Court has personal jurisdiction over Qilu for the additional reasons set forth below, and for other reasons that will be presented to the Court if such jurisdiction is challenged.

11. This Court has personal jurisdiction over Qilu Pharmaceutical Co., Ltd. because, upon information and belief, *inter alia*, it: (1) has purposely availed itself of the privilege of doing business in this Judicial District including, *inter alia*, through its subsidiary, agent and alter ego, Qilu Pharma, Inc., a company organized and existing under the laws of the State of Pennsylvania, with its principal place of business in this Judicial District at 101 Lindenwood Drive, Suite 225, Malvern, PA 19355; and (2) maintains extensive systematic contacts with the State of Pennsylvania, including the marketing, distribution, and/or sale of generic pharmaceutical drugs to Pennsylvania residents including through, *inter alia*, Qilu Pharma, Inc.

12. Alternatively, to the extent the above facts do not establish personal jurisdiction over Qilu Pharmaceutical Co., Ltd., this Court may exercise jurisdiction over Qilu Pharmaceutical Co., Ltd. pursuant to Federal Rule of Civil Procedure 4(k)(2) because: (a)

Plaintiffs' claims arise under federal law; (b) Qilu Pharmaceutical Co., Ltd. would be a foreign defendant not subject to personal jurisdiction in the courts of any state; and (c) Qilu Pharmaceutical Co., Ltd. has sufficient contacts with the United States as a whole, including, but not limited to, manufacturing and selling generic pharmaceutical products that are distributed throughout the United States, such that this Court's exercise of jurisdiction over Qilu Pharmaceutical Co., Ltd. satisfies due process.

13. This Court also has personal jurisdiction over Qilu Pharma, Inc. because, upon information and belief, *inter alia*, it: (1) is a company organized and existing under the laws of the State of Pennsylvania; (2) has its principal place of business in this Judicial District at 101 Lindenwood Drive, Suite 225, Malvern, PA 19355; and (3) engages in persistent conduct within the State of Pennsylvania and maintains extensive systematic contacts with the State of Pennsylvania, including the marketing, distribution, and/or sale of generic pharmaceutical drugs to Pennsylvania residents.

#### **THE PATENTS-IN-SUIT**

14. On May 24, 2011, the '724 patent, titled "Liquid Pharmaceutical Formulations of Palonosetron," was duly and legally issued to Plaintiffs as assignees. A copy of the '724 patent is attached as Exhibit A.

15. On May 20, 2014, the '094 patent, titled "Liquid Pharmaceutical Formulations of Palonosetron," was duly and legally issued to Plaintiffs as assignees. A copy of the '094 patent is attached as Exhibit B.

16. On June 30, 2015, the '980 patent, titled "Liquid Pharmaceutical Formulations of Palonosetron," was duly and legally issued to Plaintiffs as assignees. A copy of the '980 patent is attached as Exhibit C.

17. On November 3, 2015, the '942 patent, titled "Liquid Pharmaceutical Formulations of Palonosetron," was duly and legally issued to Plaintiffs as assignees. A copy of the '942 patent is attached as Exhibit D.

18. Pursuant to 21 U.S.C. § 355(b)(1), the '724 patent, the '094 patent, the '980 patent, and the '942 patent are listed in the United States Food and Drug Administration ("FDA") publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (also known as the "Orange Book") as covering Helsinn's Aloxi<sup>®</sup> brand palonosetron hydrochloride intravenous solutions.

### **ACTS GIVING RISE TO THIS ACTION**

#### **COUNT I – INFRINGEMENT OF THE '724 PATENT**

19. Plaintiffs reallege paragraphs 1-18 as if fully set forth herein.

20. Upon information and belief, Qilu submitted ANDA No. 20-5648 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA No. 20-5648 seeks the FDA approval necessary to engage in the commercial manufacture, use, sale, offer for sale, and/or importation of generic 0.25 mg / 5 mL and 0.075 mg / 1.5 mL palonosetron hydrochloride intravenous solutions prior to the expiration of certain of Plaintiffs' Orange Book listed patents that have the same expiration date as the '724 patent. ANDA No. 20-5648 specifically seeks FDA approval to market a generic version of Helsinn's Aloxi<sup>®</sup> brand 0.25 mg / 5 mL and 0.075 mg / 1.5 mL palonosetron hydrochloride intravenous solutions prior to the expiration of the '724 patent.

21. Upon information and belief, ANDA No. 20-5648 includes a certification under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '724 patent are invalid.

22. Qilu's submission to the FDA of ANDA No. 20-5648, including the § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '724 patent under 35 U.S.C. § 271(e)(2)(A).

23. Qilu Pharmaceutical Co., Ltd. and Qilu Pharma, Inc. are jointly and severally liable for any infringement of the '724 patent. This is because, upon information and belief, Qilu Pharmaceutical Co., Ltd. and Qilu Pharma, Inc. actively and knowingly caused to be submitted, assisted with, participated in, contributed to, and/or directed the submission of ANDA No. 20-5648 and the § 505(j)(2)(A)(vii)(IV) allegations to the FDA.

24. Qilu's active and knowing participation in, contribution to, aiding, abetting, and/or inducement of the submission to the FDA of ANDA No. 20-5648 and the § 505(j)(2)(A)(vii)(IV) certification constitutes infringement of the '724 patent under 35 U.S.C. § 271 (e)(2)(A).

25. Plaintiffs are entitled to a declaration that, if Qilu commercially manufactures, uses, offers to sell, or sells its proposed generic versions of Helsinn's Aloxi<sup>®</sup> brand products within the United States, imports its proposed generic versions of Helsinn's Aloxi<sup>®</sup> brand products into the United States, and/or induces or contributes to such conduct, Qilu will infringe the '724 patent under 35 U.S.C. § 271(a), (b), and/or (c).

26. Plaintiffs will be irreparably harmed by Qilu's infringing activities unless those activities are enjoined by this Court. Plaintiffs do not have an adequate remedy at law.

## **COUNT II – INFRINGEMENT OF THE '094 PATENT**

27. Plaintiffs reallege paragraphs 1-26 as if fully set forth herein.

28. Upon information and belief, Qilu submitted ANDA No. 20-5648 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA

No. 20-5648 seeks the FDA approval necessary to engage in the commercial manufacture, use, sale, offer for sale, and/or importation of generic 0.25 mg / 5 mL and 0.075 mg / 1.5 mL palonosetron hydrochloride intravenous solutions prior to the expiration of certain of Plaintiffs' Orange Book listed patents that have the same expiration date as the '094 patent. ANDA No. 20-5648 specifically seeks FDA approval to market a generic version of Helsinn's Aloxi<sup>®</sup> brand 0.25 mg / 5 mL and 0.075 mg / 1.5 mL palonosetron hydrochloride intravenous solutions prior to the expiration of the '094 patent.

29. Upon information and belief, ANDA No. 20-5648 includes a certification under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '094 patent are invalid.

30. Qilu's submission to the FDA of ANDA No. 20-5648, including the § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '094 patent under 35 U.S.C. § 271(e)(2)(A).

31. Qilu Pharmaceutical Co., Ltd. and Qilu Pharma, Inc. are jointly and severally liable for any infringement of the '094 patent. This is because, upon information and belief, Qilu Pharmaceutical Co., Ltd. and Qilu Pharma, Inc. actively and knowingly caused to be submitted, assisted with, participated in, contributed to, and/or directed the submission of ANDA No. 20-5648 and the § 505(j)(2)(A)(vii)(IV) allegations to the FDA.

32. Qilu's active and knowing participation in, contribution to, aiding, abetting, and/or inducement of the submission to the FDA of ANDA No. 20-5648 and the § 505(j)(2)(A)(vii)(IV) certification constitutes infringement of the '094 patent under 35 U.S.C. § 271 (e)(2)(A).

33. Plaintiffs are entitled to a declaration that, if Qilu commercially manufactures, uses, offers to sell, or sells its proposed generic versions of Helsinn's Aloxi<sup>®</sup> brand products within the United States, imports its proposed generic versions of Helsinn's Aloxi<sup>®</sup> brand products into the United States, and/or induces or contributes to such conduct, Qilu will infringe the '094 patent under 35 U.S.C. § 271(a), (b), and/or (c).

34. Plaintiffs will be irreparably harmed by Qilu's infringing activities unless those activities are enjoined by this Court. Plaintiffs do not have an adequate remedy at law.

### **COUNT III – INFRINGEMENT OF THE '980 PATENT**

35. Plaintiffs reallege paragraphs 1-34 as if fully set forth herein.

36. Upon information and belief, Qilu submitted ANDA No. 20-5648 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA No. 20-5648 seeks the FDA approval necessary to engage in the commercial manufacture, use, sale, offer for sale, and/or importation of generic 0.25 mg / 5 mL and 0.075 mg / 1.5 mL palonosetron hydrochloride intravenous solutions prior to the expiration of certain of Plaintiffs' Orange Book listed patents that have the same expiration date as the '980 patent. ANDA No. 20-5648 specifically seeks FDA approval to market a generic version of Helsinn's Aloxi<sup>®</sup> brand 0.25 mg / 5 mL and 0.075 mg / 1.5 mL palonosetron hydrochloride intravenous solutions prior to the expiration of the '980 patent.

37. Upon information and belief, ANDA No. 20-5648 includes a certification under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '980 patent are invalid.



38. Qilu's submission to the FDA of ANDA No. 20-5648, including the § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '980 patent under 35 U.S.C. § 271(e)(2)(A).

39. Qilu Pharmaceutical Co., Ltd. and Qilu Pharma, Inc. are jointly and severally liable for any infringement of the '980 patent. This is because, upon information and belief, Qilu Pharmaceutical Co., Ltd. and Qilu Pharma, Inc. actively and knowingly caused to be submitted, assisted with, participated in, contributed to, and/or directed the submission of ANDA No. 20-5648 and the § 505(j)(2)(A)(vii)(IV) allegations to the FDA.

40. Qilu's active and knowing participation in, contribution to, aiding, abetting, and/or inducement of the submission to the FDA of ANDA No. 20-5648 and the § 505(j)(2)(A)(vii)(IV) certification constitutes infringement of the '980 patent under 35 U.S.C. § 271 (e)(2)(A).

41. Plaintiffs are entitled to a declaration that, if Qilu commercially manufactures, uses, offers to sell, or sells its proposed generic versions of Helsinn's Aloxi<sup>®</sup> brand products within the United States, imports its proposed generic versions of Helsinn's Aloxi<sup>®</sup> brand products into the United States, and/or induces or contributes to such conduct, Qilu will infringe the '980 patent under 35 U.S.C. § 271(a), (b), and/or (c).

42. Plaintiffs will be irreparably harmed by Qilu's infringing activities unless those activities are enjoined by this Court. Plaintiffs do not have an adequate remedy at law.

#### **COUNT IV – INFRINGEMENT OF THE '942 PATENT**

43. Plaintiffs reallege paragraphs 1-42 as if fully set forth herein.

44. Upon information and belief, Qilu submitted ANDA No. 20-5648 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA

No. 20-5648 seeks the FDA approval necessary to engage in the commercial manufacture, use, sale, offer for sale, and/or importation of generic 0.25 mg / 5 mL and 0.075 mg / 1.5 mL palonosetron hydrochloride intravenous solutions prior to the expiration of certain of Plaintiffs' Orange Book listed patents that have the same expiration date as the '942 patent. ANDA No. 20-5648 specifically seeks FDA approval to market a generic version of Helsinn's Aloxi<sup>®</sup> brand 0.25 mg / 5 mL and 0.075 mg / 1.5 mL palonosetron hydrochloride intravenous solutions prior to the expiration of the '942 patent.

45. The '942 patent had not issued at the time Qilu made its § 505(j)(2)(A)(vii)(IV) certification regarding Plaintiffs' other Orange Book-listed patents.

46. Upon information and belief, Qilu is required by law to either amend its ANDA to contain a § 505(j)(2)(A)(vii)(IV) certification with respect to the '942 patent, or must relinquish its request that the FDA approve ANDA No. 20-5648 prior to the expiration of Plaintiffs' Orange Book-listed patents.

47. Qilu continues to seek approval of ANDA No. 20-5648 from the FDA and intends to continue in the commercial manufacture, use, sale, offer for sale, and/or importation of generic 0.25 mg / 5 mL and 0.075 mg / 1.5 mL palonosetron hydrochloride intravenous solutions prior to the expiration of the '942 patent.

48. By seeking approval of its ANDA to engage in the commercial manufacture, use, safe, offer for sale, and/or importation of generic 0.25 mg / 5 mL and 0.075 mg / 1.5 mL palonosetron hydrochloride intravenous solutions prior to the expiration of the '942 patent, Qilu infringed that patent pursuant to 35 U.S.C. § 271 (e)(2)(A).

49. Qilu Pharmaceutical Co., Ltd. and Qilu Pharma, Inc. are jointly and severally liable for any infringement of the '942 patent. This is because, upon information and

belief, Qilu Pharmaceutical Co., Ltd. and Qilu Pharma, Inc. actively and knowingly caused to be submitted, assisted with, participated in, contributed to, and/or directed the submission of ANDA No. 20-5648 to the FDA.

50. Qilu's active and knowing participation in, contribution to, aiding, abetting, and/or inducement of the submission to the FDA of ANDA No. 20-5648 constitutes infringement of the '942 patent under 35 U.S.C. § 271 (e)(2)(A).

51. Plaintiffs are entitled to a declaration that, if Qilu commercially manufactures, uses, offers to sell, or sells its proposed generic versions of Helsinn's Aloxi<sup>®</sup> brand products within the United States, imports its proposed generic versions of Helsinn's Aloxi<sup>®</sup> brand products into the United States, and/or induces or contributes to such conduct, Qilu will infringe the '942 patent under 35 U.S.C. § 271(a), (b), and/or (c).

52. Plaintiffs will be irreparably harmed by Qilu's infringing activities unless those activities are enjoined by this Court. Plaintiffs do not have an adequate remedy at law.

**STATEMENT REGARDING PRIOR-FILED SUIT**

53. Plaintiffs previously filed, on November 17, 2015, an action in the District of New Jersey seeking to enjoin Qilu from infringing the '724, '094, '980, and '942 patents. That action has been assigned Civil Action No. 15-8132 (MLC)(DEA) (D.N.J. Nov. 17, 2015) ("the D.N.J. Action"). The D.N.J. Action is assigned to Judge Mary L. Cooper.

54. In the D.N.J. Action, Plaintiffs alleged that the District Court for the District of New Jersey has personal jurisdiction over Qilu with regard to Plaintiffs' claim of patent infringement.

55. Judicial economy would be promoted, and Plaintiffs' choice of forum respected, if the claims related to Plaintiffs' action for infringement of the '724, '094, '980, and '942 patents are addressed by Judge Cooper in the District of New Jersey.

56. Pursuant to 21 U.S.C. § 355(j)(5)(B)(iii), a patent owner has 45 days from receipt of an ANDA Notice Letter to file suit in order to perfect its statutory right to a stay of FDA approval of an ANDA pending resolution of litigation regarding the submission of such ANDA. Plaintiffs filed this action as a further protective measure with regard to this statutory right.

57. Plaintiffs expect that personal jurisdiction will be maintained in the District of New Jersey and that the action will proceed in that forum. In that circumstance, this action would be unnecessary and will be voluntarily dismissed without prejudice in favor of continued prosecution of the D.N.J. Action, transferred to the District of New Jersey for consolidation with the D.N.J. Action, or subject to such other non-substantive disposition that would ensure maintenance of Plaintiffs' rights pursuant to 21 U.S.C. § 355(j)(5)(B)(iii).

#### **PRAYER FOR RELIEF**

**WHEREFORE**, Plaintiffs request that:

- A. A Judgment be entered declaring that Qilu has infringed the '724, '094, '980, and '942 patents by submitting ANDA No. 20-5648;
- B. An Order be issued pursuant to 35 U.S.C. § 271(e)(4)(A) that the effective date of any approval of ANDA No. 20-5648 be a date that is not earlier than the expiration dates of the '724, '094, '980, and '942 patents, or any later expiration of exclusivity for any of those patents to which Plaintiffs are or become entitled;
- C. An Order be issued that Qilu, its officers, agents, servants, and employees, and those persons in active concert or participation with either of them, are preliminarily and

permanently enjoined from commercially manufacturing, using, offering for sale, selling, and/or importing the proposed generic versions of Helsinn's Aloxi<sup>®</sup> brand products identified in this Complaint, and any other product that infringes or induces or contributes to the infringement of the '724, '094, '980, and '942 patents, prior to the expiration of any of those patents, including any extensions to which Plaintiffs are or become entitled; and

D. Plaintiffs be awarded such other and further relief as this Court deems just and proper.

Dated: December 1, 2015

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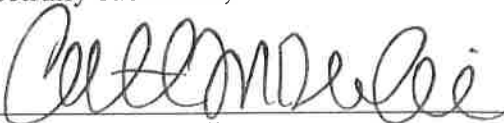
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# **Exhibit A**



US007947724B2

(12) **United States Patent**  
**Calderari et al.**(10) **Patent No.:** US 7,947,724 B2  
(45) **Date of Patent:** \*May 24, 2011(54) **LIQUID PHARMACEUTICAL**  
**FORMULATIONS OF PALONOSETRON**(75) Inventors: **Giorgio Calderari**, Rancate (CH);  
**Daniele Bonadeo**, Varese (IT); **Roberta**  
**Cannella**, Varese (IT); **Enrico Braglia**,  
Pazzallo (CH); **Riccardo Braglia**,  
Pazzallo (CH); **Andrew Miksztal**, Palo  
Alto, CA (US); **Thomas Malefyt**,  
Carmel Valley, CA (US); **Kathleen M.**  
**Lee**, Palo Alto, CA (US)(73) Assignees: **Helsinn Healthcare S.A.**, Lugano (CH);  
**Roche Palo Alto LLC**, Palo Alto, CA  
(US)(\*) 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 dis-  
claimer.

(21) Appl. No.: 11/186,311

(22) Filed: Jul. 21, 2005

(65) **Prior Publication Data**

US 2006/0069114 A1 Mar. 30, 2006

**Related U.S. Application Data**(63) Continuation of application No.  
PCT/EP2004/000888, filed on Jan. 30, 2004.(60) Provisional application No. 60/444,351, filed on Jan.  
30, 2003.(51) **Int. Cl.**  
**A01N 43/52** (2006.01)(52) **U.S. Cl.** ..... 514/397(58) **Field of Classification Search** ..... 514/397  
See application file for complete search history.(56) **References Cited**

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(Continued)

Primary Examiner — Brandon J Fetterolf

Assistant Examiner — Shirley V Gembeh

(74) Attorney, Agent, or Firm — Amall Golden Gregory LLP; Clark G. Sullivan

(57) **ABSTRACT**

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

14 Claims, No Drawings



## US 7,947,724 B2

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## LIQUID PHARMACEUTICAL FORMULATIONS OF PALONOSETRON

The present application is a continuation of PCT/EP04/000888, filed Jan. 30, 2004, which claims priority to U.S. Provisional Application 60/444,351, filed Jan. 30, 2003. The content of these applications is incorporated herein by reference.

### BACKGROUND OF THE INVENTION

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

Emesis is a devastating consequence of cytotoxic therapy, radiotherapy, and post-operative environments that drastically affects the quality of life of people undergoing such treatments. In recent years a class of drugs referred to as 5-HT<sub>3</sub> (5-hydroxytryptamine) receptor antagonists has been developed that treat such emesis by antagonizing cerebral functions associated with the 5-HT<sub>3</sub> receptor. See *Drugs Acting on 5-Hydroxytryptamine Receptors*: The Lancet Sep. 23, 1989 and references cited therein. Drugs within this class include ondansetron, granisetron, alosetron, tropisetron, and dolasetron. These 5-HT<sub>3</sub> antagonists are often administered intravenously shortly before chemotherapy or radiotherapy is initiated, and can be administered more than once during a cycle of chemotherapy or radiotherapy. In addition, they are often supplied as tablets or oral elixirs to either supplement an intravenous administration, or to ease home usage of the drug if the patient is self-administering the chemotherapeutic regimen.

Because some chemotherapeutic agents can induce emesis over extended periods of several days even when they are administered only once, it would be desirable to administer an emesis-inhibiting drug such as a 5-HT<sub>3</sub> antagonist every day until the risk of emesis has substantially subsided. The present class of 5-HT<sub>3</sub> antagonists has not proven especially helpful meeting this need, however, because the 5-HT<sub>3</sub> receptor antagonists currently marketed have proven to be less effective in controlling delayed nausea and vomiting than they are at controlling acute emesis. Sabra, K, *Choice of a 5HT<sub>3</sub> Receptor Antagonist for the Hospital Formulary*. BHP, October 1996;2 (suppl 1):S19-24.

Recently, clinical investigations have been made concerning palonosetron, a new 5-HT<sub>3</sub> receptor antagonist reported in U.S. Pat. No. 5,202,333. These investigations have shown that the drug is an order of magnitude more potent than most existing 5-HT<sub>3</sub> receptor antagonists, has a surprising half-life of about 40 hours, and is effective to reduce delayed-onset nausea induced by chemotherapeutic agents. However, formulating palonosetron in liquid formulations has not proven an easy task, typically due to shelf-stability issues. U.S. Pat. No. 5,202,333 discloses an intravenous formulation of palonosetron in example 13 that contains the following ingredients:

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

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

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

Granisetron, its uses, and medicaments made with granisetron are disclosed in U.S. Pat. Nos. 4,886,808, 4,937,247, 5,034,398 and 6,294,548. Commercially it is distributed by Roche Laboratories Inc. as Kytril®, indicated for the prevention of nausea and vomiting associated with chemotherapy or radiation therapy, and is offered in tablet form, oral solution, and as an injection.

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

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

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

Therefore, there exists a need for a palonosetron formulation with increased stability and thereby increased shelf life. There also exists a need for an appropriate range of concentrations for both the 5-HT<sub>3</sub> receptor antagonist and its pharmaceutically acceptable carriers that would facilitate making a formulation with this increased stability.

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

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

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

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

### SUMMARY OF THE INVENTION

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

In one aspect, the inventors have discovered that formulations which include the active ingredient palonosetron require in some instances only 1/10<sup>th</sup> the amount of other previously known compounds for treating emesis, which surprisingly allows the use of concentrations of palonosetron far below

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those that would ordinarily be expected. Thus, in one embodiment the invention provides a pharmaceutically stable solution for preventing or reducing emesis comprising a) from about 0.01 mg/mL to about 5 mg/mL palonosetron or a pharmaceutically acceptable salt thereof; and b) a pharmaceutically acceptable carrier.

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

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

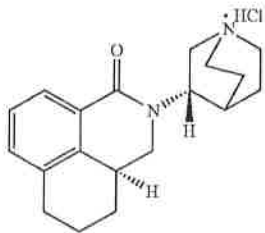
#### DETAILED DESCRIPTION OF THE INVENTION

##### Definitions

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

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

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



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

"Pharmaceutically acceptable" means that which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes that which is acceptable for veterinary use as well as human pharmaceutical use.

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

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

##### Discussion

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

A particular advantage associated with the lower dosages of intravenous palonosetron is the ability to administer the drug in a single intravenous bolus over a short, discrete time period. This time period generally extends from about 10 to about 60 seconds, or about 10 to about 40 seconds, and most preferably is about 10 to 30 seconds. In one particular embodiment the palonosetron is supplied in vials that com-

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prise 5 ml. of solution, which equates to about 0.25 mg of palonosetron at a concentration of about 0.05 mg/ml.

The inventors have further discovered that by adjusting the formulation's pH and/or excipient concentrations it is possible to increase the stability of palonosetron formulations. Therefore, in another embodiment, the invention provides a pharmaceutically stable solution for preventing or reducing emesis comprising a) palonosetron or a pharmaceutically acceptable salt thereof; and b) a pharmaceutically acceptable carrier, at a pH from about 4.0 to about 6.0. Similarly, in another embodiment the invention provides a method of formulating a pharmaceutically stable solution of palonosetron comprising admixing a) palonosetron or a pharmaceutically acceptable salt thereof; and b) a pharmaceutically acceptable carrier, at a pH from about 4.0 to about 6.0. In alternative embodiments, the pH is from about 4.5 to about 5.5, and most optimally about 5.0. There are many examples to those of skill in the art of suitable solutions to adjust the pH of a formulation. Two exemplary solutions are sodium hydroxide and hydrochloric acid solution, either of which could be used to adjust the pH of the formulation.

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

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

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

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

The inventors have further discovered that the addition of mannitol and a chelating agent can increase the stability of palonosetron formulations. Therefore, in still another embodiment the invention provides a pharmaceutically stable solution for preventing or reducing emesis comprising a) palonosetron or a pharmaceutically acceptable salt thereof and b) a pharmaceutically acceptable carrier, wherein the pharmaceutically acceptable carrier comprises a chelating agent and mannitol. Similarly, in another embodiment the invention provides a method of formulating a pharmaceutically stable solution of palonosetron comprising admixing a) palonosetron or a pharmaceutically acceptable salt thereof and b) a pharmaceutically acceptable carrier, wherein the pharmaceutically acceptable carrier comprises a chelating agent and mannitol. The chelating agent is preferably EDTA, and, in various embodiments the chelating agent is present in a concentration of from about 0.005 to about 1.0 mg/mL or from about 0.05 mg/mL to about 1.0 mg/mL or from about 0.3

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to about 0.7 mg/ml, or most optimally about 0.5 mg/ml. In various embodiments the mannitol is present in a concentration of from about 10.0 mg/ml to about 80.0 mg/ml, from about 20.0 mg/mL to about 60.0 mg/ml, or from about 40.0 to about 45.0 mg/ml.

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

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

Still further embodiments relate to improvements in the ease with which the palonosetron formulation can be stored or manufactured. In particular, the inventors have discovered that the formulations of the present invention allow storage of the product for extended periods at room temperature. Thus, in yet another embodiment the invention provides a method of storing one or more containers in which are contained a solution of palonosetron or a pharmaceutically acceptable salt thereof comprising: a) providing a room comprising said one or more containers; b) adjusting or maintaining the temperature of the room at greater than about ten, 15, or 20 degrees celcius; and c) storing said containers in said room for one month, 3 months, 6 months, one year, 18 months, 24 months or more (but preferably not exceeding 36 months), wherein (i) the palonosetron or pharmaceutical salt thereof is present in a concentration of from about 0.01 mg/mL to about 5.0 mg/mL, (ii) the pH of the solution is from about 4.0 to about 6.0, (iii) the solution comprises from about 0.01 to about 5.0 mg/ml palonosetron or a pharmaceutically acceptable salt thereof, from about 10 to about 100 millimoles citrate buffer and from about 0.005 to about 1.0 mg/ml EDTA, (iv) the solution comprises a chelating agent, or (v) the solution comprises from about 10 to about 100 millimoles of a citrate buffer.

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

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mg/ml EDTA, (iv) the solution comprises a chelating agent, or (v) the solution comprises from about 10 to about 100 milliMoles of a citrate buffer.

EXAMPLES

Example 1

Stabilizing pH

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

Example 2

Stabilizing Concentration Ranges

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

Example 3

Tonicifying Agent

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

Example 4

Formulation I

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

Ingredient	mg/mL
Palonosetron Hydrochloride	0.05*
Mannitol	41.5
EDTA	0.5
Trisodium citrate	3.7
Citric acid	1.56
WFJ	q.s. to 1 ml
Sodium hydroxide solution and/or hydrochloric acid solution	pH 5.0 ± 0.5

\*calculated as a free base

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Example 5

Formulation II

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

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

\*calculated as a free base

Example 6

Stability of Palonosetron without Dexamethasone

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

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

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

Example 7

Stability of Palonosetron with Dexamethasone

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

Test samples of palonosetron HCl 5 µg/mL with dexamethasone (as sodium phosphate) 0.2 mg/mL and also 0.4 mg/mL were prepared in polyvinyl chloride (PVC) minibags

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of each infusion solution. Additionally, palonosetron HCl 25 µg/mL with dexamethasone (as sodium phosphate) 0.33 mg/mL in each infusion solution were prepared as 10 mL of test solution in 20-mL polypropylene syringes. Evaluations for physical and chemical stability were performed on samples taken initially and after 1, 3, 7, and 14 days of storage at 4° C. and after 1, 4, 24, and 48 hours at 23° C. Physical stability was assessed using visual observation in normal room light and using a high-intensity monodirectional light beam. In addition, turbidity and particle content were measured electronically. Chemical stability of the drug was evaluated by using a stability-indicating high performance liquid chromatographic (HPLC) analytical technique.

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

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

What is claimed is:

1. A pharmaceutically stable intravenous solution for reducing emesis or reducing the likelihood of emesis comprising:

- a) from 0.03 mg/ml to 0.2 mg/ml palonosetron or a pharmaceutically acceptable salt thereof, buffered at a pH of from 4.0 to 6.0; and
- b) a pharmaceutically acceptable sterile aqueous carrier including a tonicifying effective amount of mannitol and from 0.005 mg/ml to 1.0 mg/ml EDTA.

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2. The solution of claim 1 wherein the palonosetron or pharmaceutically acceptable salt thereof is in concentration of about 0.05 mg/ml.

3. The solution of claim 1 comprising palonosetron hydrochloride.

4. The solution of claim 1 wherein the pH is from 4.5 to 5.5.

5. The solution of claim 1 wherein the pharmaceutically acceptable carrier comprises from 10 to 100 millimoles of a citrate buffer.

6. The solution of claim 1 comprising 0.3 to 0.7 mg/ml EDTA, and from 10 to 40 millimoles of a citrate buffer.

7. The solution of claim 1 comprising 0.3 to 0.7 mg/ml EDTA, from 10.0 to 80.0 mg/ml mannitol, and from 10 to 40 millimoles of a citrate buffer.

8. A pharmaceutically stable isotonic intravenous solution for reducing emesis or reducing the likelihood of emesis comprising:

a) from 0.01 mg/ml to 5 mg/ml palonosetron or a pharmaceutically acceptable salt thereof, at a pH of from 4.0 to 6.0; and

b) an aqueous pharmaceutically acceptable carrier including a chelating agent.

9. The solution of claim 8 wherein the palonosetron or pharmaceutically acceptable salt thereof is in concentration of about 0.05 mg/ml.

10. The solution of claim 8 comprising palonosetron hydrochloride.

11. The solution of claim 8 wherein the pH is from 4.5 to 5.5.

12. The solution of claim 8 wherein the pharmaceutically acceptable carrier comprises from 0.005 mg/ml to 1.0 mg/ml EDTA.

13. The solution of claim 8 wherein the pharmaceutically acceptable carrier comprises mannitol.

14. The solution of claim 8 adapted for intravenous administration.

\* \* \* \* \*

# **Exhibit B**



US008729094B2

(12) **United States Patent**  
**Calderari et al.**

(10) **Patent No.:** **US 8,729,094 B2**  
(45) **Date of Patent:** **\*May 20, 2014**

- (54) **LIQUID PHARMACEUTICAL FORMULATIONS OF PALONOSETRON**
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- (73) Assignees: **Helsinn Healthcare SA**, Pambio-Noranco (CH); **Roche Palo Alto LLC**, Palo Alto, CA (US)
- (\*) 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.: **13/902,132**

(22) Filed: **May 24, 2013**

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- (52) **U.S. Cl.**  
USPC ..... 514/296
- (58) **Field of Classification Search**  
USPC ..... 514/296  
See application file for complete search history.

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(57) **ABSTRACT**

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

**30 Claims, No Drawings**



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## LIQUID PHARMACEUTICAL FORMULATIONS OF PALONOSETRON

This is a continuation of U.S. Ser. No. 13/901,437, filed May 23, 2013, which is a continuation-in-part of U.S. Ser. No. 13/087,012 filed Apr. 14, 2011, which is a continuation of U.S. Ser. No. 11/186,311 filed Jul. 21, 2005 (now U.S. Pat. No. 7,947,724), which is a continuation of PCT/EPO4/000888, filed Jan. 30, 2004, which claims priority to U.S. Provisional Application 60/444,351, filed Jan. 30, 2003. The content of these applications is incorporated herein by reference.

### FIELD OF THE INVENTION

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

### BACKGROUND OF THE INVENTION

Emesis is a devastating consequence of cytotoxic therapy, radiotherapy, and post-operative environments that drastically affects the quality of life of people undergoing such treatments. In recent years a class of drugs referred to as 5-HT<sub>3</sub> (5-hydroxytryptamine) receptor antagonists has been developed that treat such emesis by antagonizing cerebral functions associated with the 5-HT<sub>3</sub> receptor. See *Drugs Acting on 5-Hydroxytryptamine Receptors*: The Lancet Sep. 23, 1989 and references cited therein. Drugs within this class include ondansetron, granisetron, alosetron, tropisetron, and dolasetron. These 5-HT<sub>3</sub> antagonists are often administered intravenously shortly before chemotherapy or radiotherapy is initiated, and can be administered more than once during a cycle of chemotherapy or radiotherapy. In addition, they are often supplied as tablets or oral elixirs to either supplement an intravenous administration, or to ease home usage of the drug if the patient is self-administering the chemotherapeutic regimen.

Because some chemotherapeutic agents can induce emesis over extended periods of several days even when they are administered only once, it would be desirable to administer an emesis-inhibiting drug such as a 5-HT<sub>3</sub> antagonist every day until the risk of emesis has substantially subsided. The present class of 5-HT<sub>3</sub> antagonists has not proven especially helpful meeting this need, however, because the 5-HT<sub>3</sub> receptor antagonists currently marketed have proven to be less effective in controlling delayed nausea and vomiting than they are at controlling acute emesis. Sabra, K, *Choice of a 5HT<sub>3</sub> Receptor Antagonist for the Hospital Formulary*. EHP, October 1996; 2 (suppl 1):S19-24.

Recently, clinical investigations have been made concerning palonosetron, a new 5-HT<sub>3</sub> receptor antagonist reported in U.S. Pat. No. 5,202,333. These investigations have shown that the drug is an order of magnitude more potent than most existing 5-HT<sub>3</sub> receptor antagonists, has a surprising half-life of about 40 hours, and is effective to reduce delayed-onset nausea induced by chemotherapeutic agents. However, formulating palonosetron in liquid formulations has not proven an easy task, typically due to shelf-stability issues. U.S. Pat. No. 5,202,333 discloses an intravenous formulation of palonosetron in example 13 that contains the following ingredients:

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

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

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

Granisetron, its uses, and medicaments made with granisetron are disclosed in U.S. Pat. Nos. 4,886,808, 4,937,247, 5,034,398 and 6,294,548. Commercially it is distributed by Roche Laboratories Inc. as Kytrel®. Indicated for the prevention of nausea and vomiting associated with chemotherapy or radiation therapy, and is offered in tablet form, oral solution, and as an injection.

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

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

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

Therefore, there exists a need for a palonosetron formulation with increased stability and thereby increased shelf life. There also exists a need for an appropriate range of concentrations for both the 5-HT<sub>3</sub> receptor antagonist and its pharmaceutically acceptable carriers that would facilitate making a formulation with this increased stability.

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

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

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

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

### SUMMARY OF THE INVENTION

The inventors have made a series of discoveries that support a surprisingly effective and versatile formulation for the treatment and prevention of emesis using palonosetron.

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These formulations are shelf stable for periods greater than 24 months at room temperature, and thus can be stored without refrigeration, and manufactured using non-aseptic, terminal sterilization processes.

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

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

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

#### DETAILED DESCRIPTION OF THE INVENTION

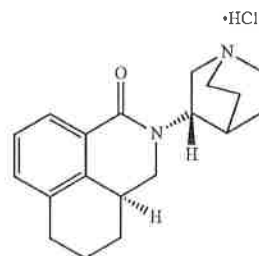
##### Definitions

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

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

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

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

"Pharmaceutically acceptable" means that which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes that which is acceptable for veterinary use as well as human pharmaceutical use.

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

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

##### Discussion

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



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a pharmaceutically acceptable carrier. In alternative embodiments, the formulation includes palonosetron or a pharmaceutically acceptable salt thereof in a concentration from about 0.02 mg/mL to about 1.0 mg/mL, from about 0.03 mg/mL to about 0.2 mg/mL, and most optimally about 0.05 mg/ml.

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

The inventors have further discovered that by adjusting the formulation's pH and/or excipient concentrations it is possible to increase the stability of palonosetron formulations. Therefore, in another embodiment, the invention provides a pharmaceutically stable solution for preventing or reducing emesis comprising a) palonosetron or a pharmaceutically acceptable salt thereof; and b) a pharmaceutically acceptable carrier, at a pH from about 4.0 to about 6.0. Similarly, in another embodiment the invention provides a method of formulating a pharmaceutically stable solution of palonosetron comprising admixing a) palonosetron or a pharmaceutically acceptable salt thereof; and b) a pharmaceutically acceptable carrier, at a pH from about 4.0 to about 6.0. In alternative embodiments, the pH is from about 4.5 to about 5.5, and most optimally about 5.0. There are many examples to those of skill in the art of suitable solutions to adjust the pH of a formulation. Two exemplary solutions are sodium hydroxide and hydrochloric acid solution, either of which could be used to adjust the pH of the formulation.

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

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

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

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

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

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

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

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

Still further embodiments relate to improvements in the ease with which the palonosetron formulation can be stored or manufactured. In particular, the inventors have discovered that the formulations of the present invention allow storage of the product for extended periods at room temperature. Thus, in yet another embodiment the invention provides a method of storing one or more containers in which are contained a solution of palonosetron or a pharmaceutically acceptable salt thereof comprising: a) providing a room comprising said one or more containers; b) adjusting or maintaining the temperature of the room at greater than about ten, 15, or 20 degrees celcius; and c) storing said containers in said room for one month, 3 months, 6 months, one year, 18 months, 24 months or more (but preferably not exceeding 36 months), wherein (i) the palonosetron or pharmaceutical salt thereof is present in a concentration of from about 0.01 mg/mL to about 5.0 mg/mL, (ii) the pH of the solution is from about 4.0 to about 6.0, (iii) the solution comprises from about 0.01 to about 5.0 mg/ml palonosetron or a pharmaceutically acceptable salt thereof, from about 10 to about 100 millimoles citrate buffer and from about 0.005 to about 1.0 mg/ml EDTA, (iv) the solution comprises a chelating agent, or (v) the solution comprises from about 10 to about 100 millimoles of a citrate buffer.

The stability of the foregoing formulations also lends itself well to terminal sterilization processes in the manufacturing process. Therefore, in still another embodiment the invention provides a method of filling a container in which is contained a solution of palonosetron or a pharmaceutically acceptable

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salt thereof comprising: a) providing one or more sterile open containers (preferably 5 ml. vials); b) filling said containers with a solution of palonosetron in a non-aseptic environment; c) sealing said filled containers; and d) sterilizing said sealed, filled containers, wherein (i) the palonosetron or pharmaceutical salt thereof is present in a concentration of from about 0.01 mg/mL to about 5 mg/mL, (ii) the pH of the solution is from about 4.0 to about 6.0, (iii) the solution comprises from about 0.01 to about 5.0 mg/ml palonosetron or a pharmaceutically acceptable salt thereof, from about 10 to about 100 millimoles citrate buffer and from about 0.005 to about 1.0 mg/ml EDTA, (iv) the solution comprises a chelating agent, or (v) the solution comprises from about 10 to about 100 milliMoles of a citrate buffer.

## EXAMPLES

## Example 1

## Stabilizing pH

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

## Example 2

## Stabilizing Concentration Ranges

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

## Example 3

## Tonicifying Agent

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

## Example 4

## Formulation I

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

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Ingredient	mg/mL
Palonosetron Hydrochloride	0.05*
Mannitol	41.5
EDTA	0.5
Trisodium citrate	3.7
Citric acid	1.56
WFJ	q.s. to 1 ml
Sodium hydroxide solution and/or hydrochloric acid solution	pH 5.0 ± 0.5

\*calculated as a free base

## Example 5

## Formulation II

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

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

\*calculated as a free base

## Example 6

## Stability of Palonosetron without Dexamethasone

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

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

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

## Example 7

## Stability of Palonosetron with Dexamethasone

The physical and chemical stability of palonosetron HCl 0.25 mg admixed with dexamethasone (as sodium phosphate)

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

Test samples of palonosetron HCl 5 µg/mL with dexamethasone (as sodium phosphate) 0.2 mg/mL and also 0.4 mg/mL were prepared in polyvinyl chloride (PVC) minibags of each infusion solution. Additionally, palonosetron HCl 25 µg/mL with dexamethasone (as sodium phosphate) 0.33 mg/mL in each infusion solution were prepared as 10 mL of test solution in 20-mL polypropylene syringes. Evaluations for physical and chemical stability were performed on samples taken initially and after 1, 3, 7, and 14 days of storage at 4° C. and after 1, 4, 24, and 48 hours at 23° C. Physical stability was assessed using visual observation in normal room light and using a high-intensity monodirectional light beam. In addition, turbidity and particle content were measured electronically. Chemical stability of the drug was evaluated by using a stability-indicating high performance liquid chromatographic (HPLC) analytical technique.

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

#### Example 8

#### Formulation III

The following is a representative pharmaceutical formulation and container closure for palonosetron that is useful for intravenous infusion formulations.

Ingredient	Amount (mg)
Palonosetron Hydrochloride	0.75 <sup>a)</sup>
Sodium Chloride	450.0
EDTA	2.5
Sodium citrate	18.5
Citric acid monohydrate	7.8
WFJ	q.s. to 50 mL
Sodium hydroxide solution and/or hydrochloric acid solution	pH 4.8 ± 0.5
Container closure system	plastic container <sup>b)</sup> plus rubber stopper <sup>c)</sup>

<sup>a)</sup>Calculated based on the weight of free base.

<sup>b)</sup>Polyethylene multilayer film infusion bag.

<sup>c)</sup>Isoprene rubber stopper.

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

What is claimed is:

1. A method for reducing the likelihood of cancer chemotherapy-induced nausea and vomiting, comprising intravenously administering to a human in need thereof a pharmaceutical single-use, unit-dose formulation comprising a 5 mL sterile aqueous isotonic solution buffered at a pH of about 5.0±0.5, said solution comprising:

about 0.05 mg/mL palonosetron hydrochloride based on the weight of its free base;

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about 41.5 mg/mL mannitol;  
about 0.5 mg/mL EDTA; and  
a citrate buffer,  
wherein said formulation is stable at 24 months when stored at room temperature, and  
wherein said intravenous administration to said human occurs before the start of the cancer chemotherapy.

2. The method of claim 1, wherein said intravenous administration to said human occurs over a period of time of 10 to 60 seconds.

3. The method of claim 1, wherein said intravenous administration reduces the likelihood of acute nausea and vomiting in said human.

4. The method of claim 1, wherein said intravenous administration reduces the likelihood of delayed nausea and vomiting in said human.

5. A method for reducing the likelihood of cancer chemotherapy-induced nausea and vomiting, comprising intravenously administering to a human in need thereof a pharmaceutical single-use, unit-dose formulation comprising a 5 mL sterile aqueous isotonic solution buffered at a pH of about 5.0±0.5, said solution comprising:

about 0.05 mg/mL palonosetron hydrochloride based on the weight of its free base;

from about 10 mg/mL to about 80 mg/mL mannitol; and  
from about 0.3 mg/mL to about 0.7 mg/mL EDTA;

wherein said solution optionally comprises a citrate buffer, wherein said formulation is stable at 24 months when stored at room temperature, and

wherein said intravenous administration to said human occurs before the start of the cancer chemotherapy.

6. The method of claim 5, wherein said intravenous administration to said human occurs over a period of time of 10 to 60 seconds.

7. The method of claim 5, wherein said intravenous administration reduces the likelihood of acute nausea and vomiting in said human.

8. The method of claim 5, wherein said intravenous administration reduces the likelihood of delayed nausea and vomiting in said human.

9. The method of claim 5, wherein said solution comprises from about 20 mg/mL to about 60 mg/mL mannitol.

10. The method of claim 9, wherein said solution comprises from about 40 mg/mL to about 45 mg/mL mannitol.

11. The method of claim 10, wherein said solution comprises about 41.5 mg/mL mannitol and about 0.5 mg/mL EDTA.

12. The method of claim 5, wherein said solution comprises a citrate buffer.

13. A method for reducing the likelihood of cancer chemotherapy-induced nausea and vomiting, comprising intravenously administering to a human in need thereof a pharmaceutical single-use, unit-dose formulation comprising a 5 mL sterile aqueous isotonic solution, said solution comprising:

about 0.05 mg/mL palonosetron hydrochloride based on the weight of its free base;

a tonicifying effective amount of mannitol; and  
from about 0.3 mg/mL to about 0.7 mg/mL EDTA;

wherein said solution optionally comprises a citrate buffer and optionally has a pH of from about 5.0±0.5,

wherein said formulation is stable at 24 months when stored at room temperature, and

wherein said intravenous administration to said human occurs before the start of the cancer chemotherapy.

14. The method of claim 13, wherein said intravenous administration to said human occurs over a period of time of 10 to 60 seconds.

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15. The method of claim 13, wherein said intravenous administration reduces the likelihood of acute nausea and vomiting in said human.

16. The method of claim 13, wherein said intravenous administration reduces the likelihood of delayed nausea and vomiting in said human.

17. The method of claim 13, wherein said solution comprises a citrate buffer.

18. The method of claim 13, wherein said solution is buffered at a pH of about  $5.0 \pm 0.5$ .

19. The method of claim 13, wherein said solution comprises from about 10 mg/mL to about 80 mg/mL mannitol.

20. The method of claim 19, wherein said solution comprises from about 20 mg/mL to about 60 mg/mL mannitol.

21. The method of claim 20, wherein said solution comprises about 41.5 mg/mL mannitol and about 0.5 mg/mL EDTA.

22. A method for reducing the likelihood of cancer chemotherapy-induced nausea and vomiting, comprising intravenously administering to a human in need thereof a pharmaceutical single-use, unit-dose formulation comprising a 5 mL sterile aqueous isotonic solution buffered at a pH of about  $5.0 \pm 0.5$ , said solution comprising:

about 0.05 mg/mL palonosetron hydrochloride based on the weight of its free base; and  
a tonicifying effective amount of mannitol;

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wherein said solution optionally comprises one or a combination of a citrate buffer and a chelating agent, wherein said formulation is stable at 24 months when stored at room temperature, and

wherein said intravenous administration to said human occurs before the start of the cancer chemotherapy.

23. The method of claim 22, wherein said intravenous administration to said human occurs over a period of time of 10 to 60 seconds.

24. The method of claim 22, wherein said intravenous administration reduces the likelihood of acute nausea and vomiting in said human.

25. The method of claim 22, wherein said intravenous administration reduces the likelihood of delayed nausea and vomiting in said human.

26. The method of claim 22, wherein said solution comprises a citrate buffer.

27. The method of claim 22, wherein said solution comprises a chelating agent.

28. The method of claim 27, wherein said chelating agent is EDTA.

29. The method of claim 28, wherein said solution comprises from about 0.3 mg/mL to about 0.7 mg/mL EDTA.

30. The method of claim 22, wherein said solution comprises from about 10 mg/mL to about 80 mg/mL mannitol.

\* \* \* \* \*

# **Exhibit C**



US009066980B2

(12) **United States Patent**  
**Calderari et al.**

(10) **Patent No.:** **US 9,066,980 B2**  
(45) **Date of Patent:** **\*Jun. 30, 2015**

(54) **LIQUID PHARMACEUTICAL FORMULATIONS OF PALONOSETRON**  
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(\* ) 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.: **13/902,299**

(22) Filed: **May 24, 2013**

(65) **Prior Publication Data**  
US 2013/0289065 A1 Oct. 31, 2013

**Related U.S. Application Data**  
(63) Continuation of application No. 13/901,437, filed on May 23, 2013, now Pat. No. 8,598,219, which is a continuation-in-part of application No. 13/087,012, filed on Apr. 14, 2011, now Pat. No. 8,518,981, which is a continuation of application No. 11/186,311, filed on Jul. 21, 2005, now Pat. No. 7,947,724, which is a continuation of application No. PCT/EP2004/000888, filed on Jan. 30, 2004.

(60) Provisional application No. 60/444,351, filed on Jan. 30, 2003.

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USPC ..... 514/296, 397  
See application file for complete search history.

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(57) **ABSTRACT**

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

**16 Claims, No Drawings**

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## LIQUID PHARMACEUTICAL FORMULATIONS OF PALONOSETRON

This is a continuation of U.S. Ser. No. 13/901,437, filed May 23, 2013, which is a continuation-in-part of U.S. Ser. No. 13/087,012 filed Apr. 14, 2011, which is a continuation of U.S. Ser. No. 11/186,311 filed Jul. 21, 2005 (now U.S. Pat. No. 7,947,724), which is a continuation of PCT/EP04/000888, filed Jan. 30, 2004, which claims priority to U.S. Provisional Application 60/444,351, filed Jan. 30, 2003. The content of these applications is incorporated herein by reference.

### BACKGROUND OF THE INVENTION

Emesis is a devastating consequence of cytotoxic therapy, radiotherapy, and post-operative environments that drastically affects the quality of life of people undergoing such treatments. In recent years a class of drugs referred to as 5-HT<sub>3</sub> (5-hydroxytryptamine) receptor antagonists has been developed that treat such emesis by antagonizing cerebral functions associated with the 5-HT<sub>3</sub> receptor. See *Drugs Acting on 5-Hydroxytryptamine Receptors*: The Lancet Sep. 23, 1989 and references cited therein. Drugs within this class include ondansetron, granisetron, alosetron, tropisetron, and dolasetron. These 5-HT<sub>3</sub> antagonists are often administered intravenously shortly before chemotherapy or radiotherapy is initiated, and can be administered more than once during a cycle of chemotherapy or radiotherapy. In addition, they are often supplied as tablets or oral elixirs to either supplement an intravenous administration, or to ease home usage of the drug if the patient is self-administering the chemotherapeutic regimen.

Because some chemotherapeutic agents can induce emesis over extended periods of several days even when they are administered only once, it would be desirable to administer an emesis-inhibiting drug such as a 5-HT<sub>3</sub> antagonist every day until the risk of emesis has substantially subsided. The present class of 5-HT<sub>3</sub> antagonists has not proven especially helpful meeting this need, however, because the 5-HT<sub>3</sub> receptor antagonists currently marketed have proven to be less effective in controlling delayed nausea and vomiting than they are at controlling acute emesis. Sabra, K, *Choice of a 5HT<sub>3</sub> Receptor Antagonist for the Hospital Formulary*. EHP, October 1996; 2 (suppl 1):S19-24.

Recently, clinical investigations have been made concerning palonosetron, a new 5-HT<sub>3</sub> receptor antagonist reported in U.S. Pat. No. 5,202,333. These investigations have shown that the drug is an order of magnitude more potent than most existing 5-HT<sub>3</sub> receptor antagonists, has a surprising half-life of about 40 hours, and is effective to reduce delayed-onset nausea induced by chemotherapeutic agents. However, formulating palonosetron in liquid formulations has not proven an easy task, typically due to shelf-stability issues. U.S. Pat. No. 5,202,333 discloses an intravenous formulation of palonosetron in example 13 that contains the following ingredients:

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

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

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

Granisetron, its uses, and medicaments made with granisetron are disclosed in U.S. Pat. Nos. 4,886,808, 4,937,247, 5,034,398 and 6,294,548. Commercially it is distributed by Roche Laboratories Inc. as Kytril®, indicated for the prevention of nausea and vomiting associated with chemotherapy or radiation therapy, and is offered in tablet form, oral solution, and as an injection.

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

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

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

Therefore, there exists a need for a palonosetron formulation with increased stability and thereby increased shelf life. There also exists a need for an appropriate range of concentrations for both the 5-HT<sub>3</sub> receptor antagonist and its pharmaceutically acceptable carriers that would facilitate making a formulation with this increased stability.

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

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

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

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

### SUMMARY OF THE INVENTION

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

In one aspect, the inventors have discovered that formulations which include the active ingredient palonosetron require in some instances only 1/10<sup>th</sup> the amount of other previously known compounds for treating emesis, which surprisingly allows the use of concentrations of palonosetron far below

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those that would ordinarily be expected. Thus, in one embodiment the invention provides a pharmaceutically stable solution for preventing or reducing emesis comprising a) from about 0.01 mg/mL to about 5 mg/mL palonosetron or a pharmaceutically acceptable salt thereof; and b) a pharmaceutically acceptable carrier.

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

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

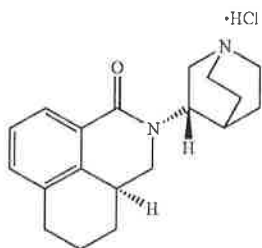
#### DETAILED DESCRIPTION OF THE INVENTION

##### Definitions

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

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

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



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

"Pharmaceutically acceptable" means that which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes that which is acceptable for veterinary use as well as human pharmaceutical use.

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

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

##### Discussion

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

A particular advantage associated with the lower dosages of intravenous palonosetron is the ability to administer the drug in a single intravenous bolus over a short, discrete time period. This time period generally extends from about 10 to about 60 seconds, or about 10 to about 40 seconds, and most

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preferably is about 10 to 30 seconds. In one particular embodiment the palonosetron is supplied in vials that comprise 5 ml. of solution, which equates to about 0.25 mg of palonosetron at a concentration of about 0.05 mg/ml.

The inventors have further discovered that by adjusting the formulation's pH and/or excipient concentrations it is possible to increase the stability of palonosetron formulations. Therefore, in another embodiment, the invention provides a pharmaceutically stable solution for preventing or reducing emesis comprising a) palonosetron or a pharmaceutically acceptable salt thereof; and b) a pharmaceutically acceptable carrier, at a pH from about 4.0 to about 6.0. Similarly, in another embodiment the invention provides a method of formulating a pharmaceutically stable solution of palonosetron comprising admixing a) palonosetron or a pharmaceutically acceptable salt thereof; and b) a pharmaceutically acceptable carrier, at a pH from about 4.0 to about 6.0. In alternative embodiments, the pH is from about 4.5 to about 5.5, and most optimally about 5.0. There are many examples to those of skill in the art of suitable solutions to adjust the pH of a formulation. Two exemplary solutions are sodium hydroxide and hydrochloric acid solution, either of which could be used to adjust the pH of the formulation.

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

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

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

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

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

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a concentration of from about 0.005 to about 1.0 mg/mL or from about 0.05 mg/mL to about 1.0 mg/mL or from about 0.3 to about 0.7 mg/ml, or most optimally about 0.5 mg/mL. In various embodiments the mannitol is present in a concentration of from about 10.0 mg/ml to about 80.0 mg/ml, from about 20.0 mg/mL to about 60.0 mg/ml, or from about 40.0 to about 45.0 mg/ml.

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

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

Still further embodiments relate to improvements in the ease with which the palonosetron formulation can be stored or manufactured. In particular, the inventors have discovered that the formulations of the present invention allow storage of the product for extended periods at room temperature. Thus, in yet another embodiment the invention provides a method of storing one or more containers in which are contained a solution of palonosetron or a pharmaceutically acceptable salt thereof comprising: a) providing a room comprising said one or more containers; b) adjusting or maintaining the temperature of the room at greater than about ten, 15, or 20 degrees celsius; and c) storing said containers in said room for one month, 3 months, 6 months, one year, 18 months, 24 months or more (but preferably not exceeding 36 months), wherein (i) the palonosetron or pharmaceutical salt thereof is present in a concentration of from about 0.01 mg/mL to about 5.0 mg/mL, (ii) the pH of the solution is from about 4.0 to about 6.0, (iii) the solution comprises from about 0.01 to about 5.0 mg/ml palonosetron or a pharmaceutically acceptable salt thereof, from about 10 to about 100 millimoles citrate buffer and from about 0.005 to about 1.0 mg/ml EDTA, (iv) the solution comprises a chelating agent, or (v) the solution comprises from about 10 to about 100 millimoles of a citrate buffer.

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

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mg/ml EDTA, (iv) the solution comprises a chelating agent, or (v) the solution comprises from about 10 to about 100 millimoles of a citrate buffer.

## EXAMPLES

## Example 1

## Stabilizing pH

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

## Example 2

## Stabilizing Concentration Ranges

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

## Example 3

## Tonicifying Agent

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

## Example 4

## Formulation I

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

Ingredient	mg/mL
Palonosetron Hydrochloride	0.05*
Mannitol	41.5
EDTA	0.5
Trisodium citrate	3.7
Citric acid	1.56
WFJ	q.s. to 1 ml
Sodium hydroxide solution and/or hydrochloric acid solution	pH 5.0 ± 0.5

\*calculated as a free base

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## Example 5

## Formulation II

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

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

\*calculated as a free base

## Example 6

## Stability of Palonosetron without Dexamethasone

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

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

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

## Example 7

## Stability of Palonosetron with Dexamethasone

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

Test samples of palonosetron HCl 5 µg/mL with dexamethasone (as sodium phosphate) 0.2 mg/mL and also 0.4 mg/mL were prepared in polyvinyl chloride (PVC) minibags of each infusion solution. Additionally, palonosetron HCl 25



µg/mL with dexamethasone (as sodium phosphate) 0.33 mg/mL in each infusion solution were prepared as 10 mL of test solution in 20-mL polypropylene syringes. Evaluations for physical and chemical stability were performed on samples taken initially and after 1, 3, 7, and 14 days of storage at 4° C. and after 1, 4, 24, and 48 hours at 23° C. Physical stability was assessed using visual observation in normal room light and using a high-intensity monodirectional light beam. In addition, turbidity and particle content were measured electronically. Chemical stability of the drug was evaluated by using a stability-indicating high performance liquid chromatographic (HPLC) analytical technique.

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

Example 8

Formulation III

The following is a representative pharmaceutical formulation and container closure for palonosetron that is useful for intravenous infusion formulations.

Ingredient	Amount (mg)
Palonosetron Hydrochloride	0.75 <sup>a)</sup>
Sodium Chloride	450.0
EDTA	2.5
Sodium citrate	18.5
Citric acid monohydrate	7.8
WFJ	q.s. to 50 mL
Sodium hydroxide solution and/or hydrochloric acid solution	pH 4.8 ± 0.5
Container closure system	plastic container <sup>b)</sup> plus rubber stopper <sup>c)</sup>

<sup>a)</sup>Calculated based on the weight of free base  
<sup>b)</sup>Polyethylene multilayer film infusion bag,  
<sup>c)</sup>Isoprene rubber stopper.

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

What is claimed is:

1. A pharmaceutical single-use, unit-dose formulation for intravenous administration to a human to reduce the likelihood of cancer chemotherapy-induced nausea and vomiting, comprising a 5 mL sterile aqueous solution, said solution comprising:

- a) palonosetron hydrochloride in an amount of 0.25 mg based on the weight of its free base,

- b) optionally a chelating agent, and
  - c) a tonicifying agent in an amount sufficient to make said solution isotonic, wherein said formulation is stable at 24 months when stored at room temperature.
2. The pharmaceutical formulation of claim 1, wherein said solution is buffered at a pH of 5.0±0.5.
  3. The pharmaceutical formulation of claim 1, wherein said tonicifying agent is mannitol.
  4. The pharmaceutical formulation of claim 3, wherein said mannitol is in an amount from 10 mg/mL to 80 mg/mL.
  5. The pharmaceutical formulation of claim 4, wherein said mannitol is in an amount of 41.5 mg/mL.
  6. The pharmaceutical formulation of claim 1, wherein said formulation comprises a chelating agent.
  7. The pharmaceutical formulation of claim 6, wherein said chelating agent is EDTA.
  8. The pharmaceutical formulation of claim 7, wherein said EDTA is in an amount of from 0.005 mg/mL to 1.0 mg/mL.
  9. The pharmaceutical formulation of claim 8, wherein said EDTA is in an amount of 0.5 mg/mL.
  10. The pharmaceutical formulation of claim 1, wherein said solution further comprises a citrate buffer.
  11. The pharmaceutical formulation of claim 10, wherein said citrate buffer is at a concentration of 20 millimolar.
  12. A method for reducing the likelihood of cancer chemotherapy-induced nausea and vomiting, comprising intravenously administering to a human in need thereof the pharmaceutical formulation of claim 1, wherein said intravenous administration to said human occurs before the start of the cancer chemotherapy.
  13. The method of claim 12, wherein said intravenous administration to said human occurs over a period of time of 10 to 60 seconds.
  14. The method of claim 12, wherein said intravenous administration reduces the likelihood of acute nausea and vomiting in said human.
  15. The method of claim 12, wherein said intravenous administration reduces the likelihood of delayed nausea and vomiting in said human.
  16. A pharmaceutical single-use, unit-dose formulation for intravenous administration to a human to reduce the likelihood of cancer chemotherapy-induced nausea and vomiting, comprising a 5 mL sterile aqueous solution, said solution comprising:
    - a) palonosetron hydrochloride in an amount of 0.25 mg based on the weight of its free base,
    - b) optionally a chelating agent, and
    - c) a tonicifying agent in an amount sufficient to make said solution isotonic, wherein said formulation is stable at 18 months when stored at room temperature.

\* \* \* \* \*

# **Exhibit D**



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(12) **United States Patent**  
**Calderari et al.**

(10) **Patent No.:** US 9,173,942 B2  
(45) **Date of Patent:** \*Nov. 3, 2015

(54) **LIQUID PHARMACEUTICAL FORMULATIONS OF PALONOSETRON**

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*A61K 47/183* (2013.01); *B65B 7/16* (2013.01);  
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(58) **Field of Classification Search**  
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See application file for complete search history.

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(\* ) 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.

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(65) **Prior Publication Data**

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(60) Provisional application No. 60/444,351, filed on Jan. 30, 2003.

(51) **Int. Cl.**  
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*A61K 31/473* (2006.01)  
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CPC ..... *A61K 47/26* (2013.01); *A61K 9/0019* (2013.01); *A61K 9/0095* (2013.01); *A61K 31/473* (2013.01); *A61K 47/00* (2013.01);

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(57) **ABSTRACT**

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

**19 Claims, No Drawings**

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**LIQUID PHARMACEUTICAL  
FORMULATIONS OF PALONOSETRON**

This is a continuation of U.S. Ser. No. 13/901,437, filed May 23, 2013, which is a continuation-in-part of U.S. Ser. No. 13/087,012 filed Apr. 14, 2011, which is a continuation of U.S. Ser. No. 11/186,311 filed Jul. 21, 2005 (now U.S. Pat. No. 7,947,724), which is a continuation of PCT/EP04/000888, filed Jan. 30, 2004, which claims priority to U.S. Provisional Application 60/444,351, filed Jan. 30, 2003. The content of these applications is incorporated herein by reference.

FIELD OF THE INVENTION

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

BACKGROUND OF THE INVENTION

Emesis is a devastating consequence of cytotoxic therapy, radiotherapy, and post-operative environments that drastically affects the quality of life of people undergoing such treatments. In recent years a class of drugs referred to as 5-HT<sub>3</sub> (5-hydroxytryptamine) receptor antagonists has been developed that treat such emesis by antagonizing cerebral functions associated with the 5-HT<sub>3</sub> receptor. See *Drugs Acting on 5-Hydroxytryptamine Receptors*; The Lancet Sep. 23, 1989 and references cited therein. Drugs within this class include ondansetron, granisetron, alosetron, tropisetron, and dolasetron. These 5-HT<sub>3</sub> antagonists are often administered intravenously shortly before chemotherapy or radiotherapy is initiated, and can be administered more than once during a cycle of chemotherapy or radiotherapy. In addition, they are often supplied as tablets or oral elixirs to either supplement an intravenous administration, or to ease home usage of the drug if the patient is self-administering the chemotherapeutic regimen.

Because some chemotherapeutic agents can induce emesis over extended periods of several days even when they are administered only once, it would be desirable to administer an emesis-inhibiting drug such as a 5-HT<sub>3</sub> antagonist every day until the risk of emesis has substantially subsided. The present class of 5-HT<sub>3</sub> antagonists has not proven especially helpful meeting this need, however, because the 5-HT<sub>3</sub> receptor antagonists currently marketed have proven to be less effective in controlling delayed nausea and vomiting than they are at controlling acute emesis. Sabra, K. *Choice of a 5HT<sub>3</sub> Receptor Antagonist for the Hospital Formulary*, EHP, October 1996; 2 (suppl 1):S19-24.

Recently, clinical investigations have been made concerning palonosetron, a new 5-HT<sub>3</sub> receptor antagonist reported in U.S. Pat. No. 5,202,333. These investigations have shown that the drug is an order of magnitude more potent than most existing 5-HT<sub>3</sub> receptor antagonists, has a surprising half-life of about 40 hours, and is effective to reduce delayed-onset nausea induced by chemotherapeutic agents. However, formulating palonosetron in liquid formulations has not proven an easy task, typically due to shelf-stability issues. U.S. Pat. No. 5,202,333 discloses an intravenous formulation of palonosetron in example 13 that contains the following ingredients:

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Ingredient	Mg
Palonosetron HCl	10-100 mg
Dextrose Monohydrate	q.s. to make isotonic
Citric Acid Monohydrate	1.05 mg
Sodium Hydroxide	0.18 mg
WFI	To 1.0 ml.

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

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

Granisetron, its uses, and medicaments made with granisetron are disclosed in U.S. Pat. Nos. 4,886,808, 4,937,247, 5,034,398 and 6,294,548. Commercially it is distributed by Roche Laboratories Inc. as Kytril<sup>®</sup>, indicated for the prevention of nausea and vomiting associated with chemotherapy or radiation therapy, and is offered in tablet form, oral solution, and as an injection.

Alosetron, its uses, and medicaments made with alosetron are disclosed in U.S. Pat. Nos. 5,360,800 and 6,284,770. Commercially it is distributed by GlaxoSmithKline as Lotronex<sup>®</sup>.

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

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

Therefore, there exists a need for a palonosetron formulation with increased stability and thereby increased shelf life. There also exists a need for an appropriate range of concentrations for both the 5-HT<sub>3</sub> receptor antagonist and its pharmaceutically acceptable carriers that would facilitate making a formulation with this increased stability.

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

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

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

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

SUMMARY OF THE INVENTION

The inventors have made a series of discoveries that support a surprisingly effective and versatile formulation for the treatment and prevention of emesis using palonosetron. These formulations are shelf stable for periods greater than 24

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months at room temperature, and thus can be stored without refrigeration, and manufactured using non-aseptic, terminal sterilization processes.

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

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

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

## DETAILED DESCRIPTION OF THE INVENTION

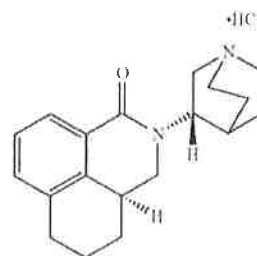
### Definitions

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

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

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

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

"Pharmaceutically acceptable" means that which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes that which is acceptable for veterinary use as well as human pharmaceutical use.

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

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

### Discussion

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

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a pharmaceutically acceptable carrier. In alternative embodiments, the formulation includes palonosetron or a pharmaceutically acceptable salt thereof in a concentration from about 0.02 mg/ml, to about 1.0 mg/ml, from about 0.03 mg/ml, to about 0.2 mg/ml, and most optimally about 0.05 mg/ml.

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

The inventors have further discovered that by adjusting the formulation's pH and/or excipient concentrations it is possible to increase the stability of palonosetron formulations. Therefore, in another embodiment, the invention provides a pharmaceutically stable solution for preventing or reducing emesis comprising a) palonosetron or a pharmaceutically acceptable salt thereof; and b) a pharmaceutically acceptable carrier, at a pH from about 4.0 to about 6.0. Similarly, in another embodiment the invention provides a method of formulating a pharmaceutically stable solution of palonosetron comprising admixing a) palonosetron or a pharmaceutically acceptable salt thereof; and b) a pharmaceutically acceptable carrier, at a pH from about 4.0 to about 6.0. In alternative embodiments, the pH is from about 4.5 to about 5.5, and most optimally about 5.0. There are many examples to those of skill in the art of suitable solutions to adjust the pH of a formulation. Two exemplary solutions are sodium hydroxide and hydrochloric acid solution, either of which could be used to adjust the pH of the formulation.

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

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

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

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

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

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

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

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

Still further embodiments relate to improvements in the ease with which the palonosetron formulation can be stored or manufactured. In particular, the inventors have discovered that the formulations of the present invention allow storage of the product for extended periods at room temperature. Thus, in yet another embodiment the invention provides a method of storing one or more containers in which are contained a solution of palonosetron or a pharmaceutically acceptable salt thereof comprising: a) providing a room comprising said one or more containers; b) adjusting or maintaining the temperature of the room at greater than about ten, 15, or 20 degrees celsius; and c) storing said containers in said room for one month, 3 months, 6 months, one year, 18 months, 24 months or more (but preferably not exceeding 36 months), wherein (i) the palonosetron or pharmaceutical salt thereof is present in a concentration of from about 0.01 mg/ml, to about 5.0 mg/ml, (ii) the pH of the solution is from about 4.0 to about 6.0, (iii) the solution comprises from about 0.01 to about 5.0 mg/ml palonosetron or a pharmaceutically acceptable salt thereof, from about 10 to about 100 millimoles citrate buffer and from about 0.005 to about 1.0 mg/ml EDTA, (iv) the solution comprises a chelating agent, or (v) the solution comprises from about 10 to about 100 millimoles of a citrate buffer.

The stability of the foregoing formulations also lends itself well to terminal sterilization processes in the manufacturing process. Therefore, in still another embodiment the invention provides a method of filling a container in which is contained a solution of palonosetron or a pharmaceutically acceptable

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salt thereof comprising: a) providing one or more sterile open containers (preferably 5 ml. vials); b) filling said containers with a solution of palonosetron in a non-aseptic environment; c) sealing said filled containers; and d) sterilizing said sealed, filled containers, wherein (i) the palonosetron or pharmaceutical salt thereof is present in a concentration of from about 0.01 mg/ml<sub>o</sub> to about 5 mg/ml<sub>o</sub>, (ii) the pH of the solution is from about 4.0 to about 6.0, (iii) the solution comprises from about 0.01 to about 5.0 mg/ml palonosetron or a pharmaceutically acceptable salt thereof, from about 10 to about 100 millimoles citrate buffer and from about 0.005 to about 1.0 mg/ml EDTA, (iv) the solution comprises a chelating agent, or (v) the solution comprises from about 10 to about 100 millimoles of a citrate buffer.

EXAMPLES

Example 1

Stabilizing pH

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

Example 2

Stabilizing Concentration Ranges

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

Example 3

Tonicifying Agent

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

Example 4

Formulation I

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

Ingredient	mg/ml
Palonosetron Hydrochloride	0.05*
Mannitol	41.5

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-continued

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

\*calculated as a free base

Example 5

Formulation II

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

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

\*calculated as a free base

Example 6

Stability of Palonosetron without Dexamethasone

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

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

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

Example 7

Stability of Palonosetron with Dexamethasone

The physical and chemical stability of palonosetron HCl 0.25 mg admixed with dexamethasone (as sodium phosphate)

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

Test samples of palonosetron HCl 5 µg/ml, with dexamethasone (as sodium phosphate) 0.2 mg/ml, and also 0.4 mg/ml, were prepared in polyvinyl chloride (PVC) minibags of each infusion solution. Additionally, palonosetron HCl 25 µg/ml, with dexamethasone (as sodium phosphate) 0.33 mg/ml, in each infusion solution were prepared as 10 mL of test solution in 20-mL polypropylene syringes. Evaluations for physical and chemical stability were performed on samples taken initially and after 1, 3, 7, and 14 days of storage at 4° C. and after 1, 4, 24, and 48 hours at 23° C. Physical stability was assessed using visual observation in normal room light and using a high-intensity monodirectional light beam. In addition, turbidity and particle content were measured electronically. Chemical stability of the drug was evaluated by using a stability-indicating high performance liquid chromatographic (HPLC) analytical technique.

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

#### Example 8

#### Formulation III

The following is a representative pharmaceutical formulation and container closure for palonosetron that is useful for intravenous infusion formulations.

Ingredient	Amount (mg)
Palonosetron Hydrochloride	0.75 <sup>(a)</sup>
Sodium Chloride	450.0
EDTA	2.5
Sodium citrate	18.5
Citric acid monohydrate	7.8
WFI	q.s. to 50 mL
Sodium hydroxide solution and/or hydrochloric acid solution	pH 4.8 ± 0.5
Container closure system	plastic container <sup>(b)</sup> plus rubber stopper <sup>(c)</sup>

<sup>(a)</sup> Calculated based on the weight of free base.

<sup>(b)</sup> Polyethylene multilayer film infusion bag.

<sup>(c)</sup> Toprene rubber stopper.

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

#### What is claimed is:

1. A formulation comprising a pharmaceutical sterile aqueous intravenous solution, wherein said pharmaceutical sterile aqueous intravenous solution comprises:

palonosetron hydrochloride or another pharmaceutically acceptable salt of palonosetron at a concentration of 0.05 mg/ml, based on the weight of the palonosetron free base; and

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from 10 mg/mL to 80 mg/mL mannitol;

wherein the pharmaceutical sterile aqueous intravenous solution has a pH of 4.0 to 6.0.

2. The formulation of claim 1, wherein said pharmaceutical sterile aqueous intravenous solution comprises palonosetron hydrochloride or another pharmaceutically acceptable salt of palonosetron is in an amount of 0.25 mg.

3. The formulation of claim 1, wherein said pharmaceutical sterile aqueous intravenous solution comprises from 20 mg/mL to 60 mg/mL mannitol.

4. The formulation of claim 1, wherein said pharmaceutical sterile aqueous intravenous solution comprises from 40 mg/mL to 45 mg/mL mannitol.

5. The formulation of claim 1, wherein said pharmaceutical sterile aqueous intravenous solution comprises 41.5 mg/mL mannitol.

6. The formulation of claim 1, wherein said pharmaceutical sterile aqueous intravenous solution comprises a chelating agent.

7. The formulation of claim 6, wherein said chelating agent is EDTA.

8. The formulation of claim 7, wherein said pharmaceutical sterile aqueous intravenous solution comprises from 0.3 mg/mL to 0.7 mg/mL EDTA.

9. The formulation of claim 7, wherein said pharmaceutical sterile aqueous intravenous solution comprises 0.5 mg/mL EDTA.

10. The formulation of claim 1, wherein said pharmaceutical sterile aqueous intravenous solution has a pH of 5.0±0.5.

11. The formulation of claim 1, wherein said pharmaceutical sterile aqueous intravenous solution comprises a citrate buffer.

12. A formulation comprising a pharmaceutical sterile aqueous intravenous solution, wherein said pharmaceutical sterile aqueous intravenous solution comprises:

palonosetron hydrochloride or another pharmaceutically acceptable salt of palonosetron at a concentration of 0.05 mg/mL, based on the weight of the palonosetron free base;

from 10 mg/mL to 80 mg/mL mannitol; and

from 0.3 mg/mL to 0.7 mg/mL EDTA.

13. The formulation of claim 12, wherein said pharmaceutical sterile aqueous intravenous solution comprises palonosetron hydrochloride or another pharmaceutically acceptable salt of palonosetron is in an amount of 0.25 mg.

14. The formulation of claim 12, wherein said pharmaceutical sterile aqueous intravenous solution has a pH of 4.0 to 6.0.

15. The formulation of claim 12, wherein said pharmaceutical sterile aqueous intravenous solution has a pH of 5.0±0.5.

16. The formulation of claim 12, wherein said pharmaceutical sterile aqueous intravenous solution comprises from 20 mg/mL to 60 mg/mL mannitol.

17. The formulation of claim 12, wherein said pharmaceutical sterile aqueous intravenous solution comprises from 40 mg/mL to 45 mg/mL mannitol.

18. The formulation of claim 12, wherein said pharmaceutical sterile aqueous intravenous solution comprises 41.5 mg/mL mannitol and 0.5 mg/mL EDTA.

19. The formulation of claim 12, wherein said pharmaceutical sterile aqueous intravenous solution comprises a citrate buffer.

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