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UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

HELSINN HEALTHCARE S.A. and ROCHE PALO ALTO LLC, Plaintiffs, v. QILU PHARMACEUTICAL CO., LTD. and QILU PHARMA, INC., 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 Pharma, Inc., has an active business entity status registered with the New Jersey Department of Treasury under the business entity identification number 0400704255, and maintains a corporate agent for service of process at 108 Carnegie Center, Suite 208, Princeton, NJ 08540.

6. 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 New Jersey.

NATURE OF THE ACTION

7. 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

8. 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.

9. 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.

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

11. 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 New Jersey, that have led to foreseeable harm and injury to Plaintiffs in the State of New Jersey. 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.

12. Qilu sent Notice Letters dated October 19, 2015 to Helsinn's two New Jersey addresses (among others), which were received by Plaintiffs on October 26, 2015 ("Notice Letters").

13. Qilu's Notice Letters state that it filed Abbreviated New Drug Application ("ANDA") No. 20-5648 seeking approval from the United States Food and Drug Administration ("FDA") to engage in the commercial manufacture, use, importation, offer for sale and sale of generic 0.25 mg / 5 mL and 0.075 mg / 1.5 mL palonosetron hydrochloride intravenous solutions in the United States (including, upon information and belief, in the State of New Jersey) prior to the expiration of the patents-in-suit.

14. This Court also 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 registered with the New Jersey Department of Treasury to do business in New Jersey under the business entity identification number 0400704255 and maintaining a corporate agent for service of process at 108 Carnegie Center, Suite 208, Princeton, NJ 08540; (2) maintains extensive systematic contacts with the State of New Jersey, including the marketing, distribution, and/or sale of generic pharmaceutical drugs to New Jersey residents including through, *inter alia*, Qilu Pharma, Inc.; and (3) as detailed above, has sent the Notice Letters into New Jersey.

15. 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.

16. This Court also has personal jurisdiction over Qilu Pharma, Inc. 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*, registering to do business in New Jersey and designating an in-state agent to receive service of process in New Jersey; (2) engages in persistent conduct within the State of New Jersey and maintains extensive systematic contacts with the State of New Jersey, including the marketing, distribution, and/or sale of generic pharmaceutical drugs to New Jersey residents; and (3) as detailed above, has sent the Notice Letters via Qilu Pharmaceutical Co., Ltd. into New Jersey.

THE PATENTS-IN-SUIT

17. 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.

18. 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.

19. 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.

20. 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.

21. Pursuant to 21 U.S.C. § 355(b)(l), 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® brand palonosetron hydrochloride intravenous solutions.

ACTS GIVING RISE TO THIS ACTION

COUNT I – INFRINGEMENT OF THE '724 PATENT

22. Plaintiffs reallege paragraphs 1-21 as if fully set forth herein.

23. 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® 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.

24. 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.

25. 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).

26. 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.

27. 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).

28. 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® brand products within the United States, imports its proposed generic versions of Helsinn's Aloxi® 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).

29. 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

30. Plaintiffs reallege paragraphs 1-29 as if fully set forth herein.

31. 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® 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.

32. 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.

33. 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).

34. 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.

35. 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).

36. 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® brand products within the United States, imports its proposed generic versions of Helsinn's

Aloxi® 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).

37. 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

38. Plaintiffs reallege paragraphs 1-37 as if fully set forth herein.

39. 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® 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.

40. 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.

41. 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).

42. 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.

43. 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).

44. 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® brand products within the United States, imports its proposed generic versions of Helsinn's Aloxi® 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).

45. 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

46. Plaintiffs reallege paragraphs 1-45 as if fully set forth herein.

47. 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® 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.

48. 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.

49. 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.

50. 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.

51. 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).

52. 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.

53. 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).

54. 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®

brand products within the United States, imports its proposed generic versions of Helsinn's Aloxi® 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).

55. 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.

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® 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: November 17, 2015

Respectfully submitted,

By: s/ Charles M. Lizza

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CERTIFICATION PURSUANT TO LOCAL CIVIL RULES 11.2 & 40.1

Pursuant to Local Civil Rules 11.2 and 40.1, I hereby certify that the matters captioned *Helsinn Healthcare S.A., et al. v. Dr. Reddy Laboratories, Ltd., et al.*, Civil Action No. 11-3962 (MLC)(DEA) (D.N.J. July 8, 2011) (Consolidated), *Helsinn Healthcare, S.A., et al. v. Dr. Reddy's Laboratories, Ltd., et al.*, Civil Action No. 12-2867 (MLC)(DEA) (D.N.J. May 11, 2012), *Helsinn Healthcare, S.A., et al. v. Dr. Reddy's Laboratories, Ltd., et al.*, Civil Action No. 14-4274 (MLC)(DEA) (D.N.J. July 7, 2014), *Helsinn Healthcare, S.A., et al. v. Teva Pharmaceuticals USA, Inc., et al.*, Civil Action No. 14-6341 (MLC)(DEA) (D.N.J. Oct. 13, 2014), *Helsinn Healthcare, S.A., et al. v. Hospira, Inc., et al.*, Civil Action No. 15-2077 (MLC)(DEA) (D.N.J. Mar. 23, 2015), *Helsinn Healthcare, S.A., et al. v. Par Pharmaceutical Companies, Inc., et al.*, Civil Action No. 15-2078 (MLC)(DEA) (D.N.J. Mar. 23, 2015), *Helsinn Healthcare, S.A., et al. v. Fresenius Kabi USA, LLC, et al.*, Civil Action No. 15-7015 (MLC)(DEA) (D.N.J. Sept. 22, 2015); *Helsinn Healthcare, S.A., et al. v. Fresenius Kabi USA, LLC, et al.*, Civil Action No. 15-7378 (MLC)(DEA) (D.N.J. Oct. 8, 2015); *Helsinn Healthcare, S.A., et al. v. Exela Pharma Sciences LLC, et al.*, Civil Action No. 14-1444 (GMS) (D. Del. Dec. 1, 2014) (currently stayed); and *Helsinn Healthcare, S.A., et al. v. Fresenius Kabi USA, LLC*, Civil Action No. 15-0865 (D. Del. Sept. 24, 2015) are related to the matter in controversy because the matter in controversy involves the same plaintiffs and the same or related patents, and because Defendants are seeking FDA approval to market generic versions of the same pharmaceutical products.

I further certify that, to the best of my knowledge, the matter in controversy is not the subject of any other action pending in any court, or of any pending arbitration or administrative proceeding.

Dated: November 17, 2015

Respectfully submitted,

By: s/ Charles M. Lizza

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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 disclaimer.

(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**

U.S. PATENT DOCUMENTS

4,695,578	A	9/1987	Coates et al.	514/397
4,753,789	A	6/1988	Tyers et al.	424/10
4,886,808	A	12/1989	King	514/299
4,906,755	A	3/1990	Gittos	546/94
4,929,632	A	5/1990	Tyers et al.	514/397
4,937,247	A	6/1990	King	514/299
5,011,846	A	4/1991	Gittos et al.	514/294
5,034,398	A	7/1991	King	514/299
5,202,333	A	4/1993	Berger et al.	514/296
5,240,954	A	8/1993	Tyers et al.	514/395
5,272,137	A	12/1993	Blase et al.	
5,344,658	A	9/1994	Collin	424/489
5,578,628	A	11/1996	Tyers et al.	514/397
5,578,632	A	11/1996	Tyers et al.	514/397
5,622,720	A	4/1997	Collin	424/489
5,854,270	A *	12/1998	Gambhir	514/397
5,922,749	A	7/1999	Tyers et al.	514/397
5,955,488	A	9/1999	Winterborn	514/399
6,063,802	A	5/2000	Winterborn	514/397
6,284,749	B1 *	9/2001	Castillo et al.	514/159
6,287,592	B1 *	9/2001	Dickinson	424/450
6,294,548	B1	9/2001	James	514/299
2001/0020029	A1	9/2001	James	514/299
2003/0095926	A1	5/2003	Dugger, III	424/43

FOREIGN PATENT DOCUMENTS

WO	WO 03/100091	A	12/2003
WO	WO-2004/045615	A1 *	6/2004
WO	WO-2004073714	A1 *	6/2004
WO	2004067005		8/2004

OTHER PUBLICATIONS

Chaitow, 1990, 3 pages.*

Eglen, R. M. et al., Pharmacological Characterization of RS 25259-197, a Novel and Selective 5-HT_3 Receptor Antagonist, in vivo, extracted from *British Journal of Pharmacology*, 1995, vol. 114, No. 4, pp. 860-866.

Chelly, Jacques et al., Oral RS-25259 Prevents Postoperative Nausea and Vomiting Following Laparoscopic Surgery, extracted from *Anesthesiology*, 1996, vol. 85, No. 3A, p. A21.

Sorbe, Bengt, 5-HT_3 Receptor Antagonists as Antiemetic Agents in Cancer Chemotherapy, extracted from *Expert Opinion on Investigational Drugs*, 1996, vol. 5, No. 4, pp. 389-407.

Gaster, Laramie M. and King, Frank D., Serotonin 5-HT_3 and 5-HT_4 Receptor Antagonists, extracted from *Medicinal Research Reviews*, 1997, vol. 17, No. 2, pp. 163-214.

Tang, Jun et al., Efficacy of RS-25259, a Novel 5-HT_3 Antagonist, in the Prevention of Postoperative Nausea and Vomiting After Major Gynecologic Surgery, abstract extracted from *Anesthesiology*, 1997, vol. 85, No. 3, suppl. p. A329.

Tang, Jun et al., The Efficacy of RS-25259, a Long-Acting Selective 5-HT_3 Receptor Antagonist, for Preventing Postoperative Nausea and Vomiting After Hysterectomy Procedures, extracted from *Anesthesia and Analgesia*, 1998, vol. 87, pp. 462-467.

Adis R&D Profile, Palonosetron RS 25259, RS 25259 197, extracted from *Drugs in R&D*, Oct. 1999, vol. 2, No. 4, pp. 251-252.

Piraccini, Gaia et al., An Interesting 5-HT_3 Receptor Antagonist Antiemetic for Patients Undergoing Chemotherapy-Based Conditioning Regimens?, extracted from *Blood*, Nov. 16, 2001, vol. 98, No. 11, part 2, p. 350b, abstract No. 5169.

(Continued)

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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.

14 Claims, No Drawings

OTHER PUBLICATIONS

Stacher, Georg, *Palonosetron Helsinn*, extracted from *Current Opinion in Investigational Drugs*, Oct. 2002, vol. 3, No. 10, pp. 1502-1507.

Navari, Rudolph M., Pathogenesis-Based Treatment of Chemotherapy-Induced Nausea and Vomiting—Two New Agents, extracted from *Journal of Supportive Oncology*, 2003, vol. 1(2), pp. 89-103.

Oppostion Brief filed by Dr. Reddy's Laboratories (UK) Limited, opposition to European Patent No. 1601359 B1, Jul. 7, 2009.

Photolytic and oxidative degradation of an antiemetic agent, RG 12915 (Won C. M. Et al, International Journal of Pharmaceutics 121 (1995) 95-105 (1995).

Palonosetron: a phase II dose ranging study to assess over a 7 day period the single dose pharmacokinetic profile of palonosetron in patients receiving highly emetogenic chemotherapy. Piraccini G et al., Proc. Am. Soc. Clin. Oncol 2002 21 Abs 449 (2002).

Formulation and administration techniques to minimize injection pain and tissue damage associated with parenteral products. Larry A. Gatlin; Carol A Brister Gatlin, from Injectable Drug Development: Techniques to Reduce Pain and Irritation [Edited by Pramod K. Gupta, Gayle A. Brazeau; Published by Informa Health Care (original copyright of 1999 by Interpharma Press), 1999; ISBN 1574910957, 9781574910957)], p. 401-421.

Parenteral Dosage Forms. Joanne Broadhead. from Part 11—Early drug development, Pharmaceutical preformulation and formulation: a practice guide from candidate drug selection to commercial dosage form [Edited by Mark Gibson; Published by Interpharma Press, 2001; ISBN 1574911201, 9781574911206)], p. 331-353.

Opposition Brief filed by Tecnimede Sociedade Tecnico-Medicinal S.A., opposition to European Patent No. 1601359 B1, Jul. 8, 2009.

Response brief filed by Helsinn Healthcare S.A. dated Jul. 13, 2007, in response to the communication pursuant to Art. 96(2) EPC of Jan. 3, 2007 regarding Serial No. 04 706 657.6-2123.

European Patent Office official communication dated Jul. 19, 2006 regarding Serial No. 04 706 657.6.

Response of Helsinn Healthcare S.A. dated Nov. 29, 2006 regarding EPO official communication dated Jul. 19, 2006.

Lachman et al., The Theory and Practice of Industrial Pharmacy, 1986, third edition, pp. 652-784.

Opposition Brief filed by Martin Paul White, opposition to European Patent No. 1601359 B1, Jul. 8, 2009.

Wong et al. (1995), in British Journal of Pharmacology, vol. 114, pp. 851-859 and Eglen et al. (1995), in British Journal of Pharmacology, vol. 114, pp. 860-866.

Cover page and pp. 642-644 and 783-784 of The Theory and Practice of Industrial Pharmacy, Third Edition, Lea and Febiger (1986).

Cover page and pp. 514-515 of Modern Pharmaceutics, Second Edition, Marcel Dekker (1990).

Cover page and pp. 142-143 of Pharmaceutical Dosage Forms: Parenteral Medications vol. 1, Second Edition, Marcel Dekker (1992).

Mitsuo Matsumoto, et al., "Yakuzaigaku Manual", 1st edition, Nanzando Co., Ltd. (1989) 2 pages.

Michael J. Pikal, "Freeze Drying", Encyclopedia of Pharmaceutical Technology, Third Edition, Jan. 2007, pp. 1824-1825, vol. 3, Informa Pharmaceuticals & Healthcare.

Daniele Bonadeo, "Supplemental Declaration of Daniele Bonadeo 37 C.F.R. 1.132", U.S. Appl. No. 11/388,270, Jun. 8, 2009.

Kranke et al. 2007, "Recent advances, trends and economic considerations in . . . " Expert Opinion Pharmacother., 8 (18): 3217-3235).

Morrow et al. 1995, Progress in reducing nausea and emesis. Comparisons of ondansetron, granisetron, and tropisetron. Cancer, vol. 76 No. 3 pp. 343-357.

USPTO Notice of Allowance and Fee Due, U.S. Appl. No. 11/388,270, filed Mar. 24, 2006, Date Mailed Jan. 26, 2010.

USPTO Office Action, U.S. Appl. No. 11/129,839, Date Mailed Jan. 15, 2010.

Israili, Zafar H., Clinical Pharmacology of Serotonin Receptor Type-3 (5-HT3) Antagonists, Curr. Med. Chem.—Central Nervous System Agents, 2001, 1, 171-199.

Barton (Citrate Buffer Calculation), 2000, 2 pages.

USPTO Office Action, U.S. Appl. No. 11/201,035, Date Mailed Aug. 19, 2009.

Response of Helsinn Healthcare to opposition of EP Serial No. 04 706 657.6 dated Feb. 11, 2010.

Annex 1 (Statement of Waldo Mossi, Ph.D.) to Response of Helsinn Healthcare to opposition of EP Serial No. 04 706 657.6 dated Feb. 11, 2010.

Annex 2 to Response of Helsinn Healthcare to opposition of EP Serial No. 04 706 657.6 dated Feb. 11, 2010.

Annex 3 to Response of Helsinn Healthcare to opposition of EP Serial No. 04 706 657.6 dated Feb. 11, 2010.

* cited by examiner

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_3 (5-hydroxytryptamine) receptor antagonists has been developed that treat such emesis by antagonizing cerebral functions associated with the 5-HT_3 receptor. See *Drugs Acting on 5-Hydroxytryptamine Receptors:* The Lancet Sep. 23, 1989 and references cited therein. Drugs within this class include ondansetron, granisetron, alosetron, tropisetron, and dolasetron. These 5-HT_3 antagonists are often administered intravenously shortly before chemotherapy or radiotherapy is initiated, and can be administered more than once during a cycle of chemotherapy or radiotherapy. In addition, they are often supplied as tablets or oral elixirs to either supplement an intravenous administration, or to ease home usage of the drug if the patient is self-administering the chemotherapeutic regimen.

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

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

Ingredient	Mg
Palonosetron 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 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® (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_3 receptor antagonist and its pharmaceutically acceptable carriers that would facilitate making a formulation with this increased stability.

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

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

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

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

SUMMARY OF THE INVENTION

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

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

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

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

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

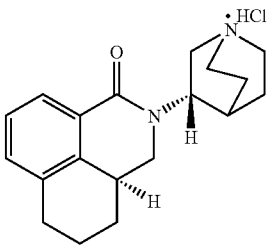
DETAILED DESCRIPTION OF THE INVENTION

Definitions

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

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

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



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

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

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

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

Discussion

The fact that palonosetron can be formulated in some instances at concentrations of only about $1/10^{th}$ 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-

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

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

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

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

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

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

EXAMPLES

Example 1

Stabilizing pH

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

Example 2

Stabilizing Concentration Ranges

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

Example 3

Tonicifying Agent

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

Example 4

Formulation I

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

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

*calculated as a free base

Example 5

Formulation II

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

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

*calculated as a free base

Example 6

Stability of Palonosetron without Dexamethasone

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

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

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

Example 7

Stability of Palonosetron with Dexamethasone

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

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

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

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

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

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.

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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(*) 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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(51) **Int. Cl.**
A61K 47/00 (2006.01)

(52) **U.S. Cl.**
USPC **514/296**

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

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,695,578	A	9/1987	Coates et al.	
4,753,789	A	6/1988	Tyers et al.	
4,886,808	A	12/1989	King	
4,906,755	A	3/1990	Gittos	
4,929,632	A	5/1990	Tyers et al.	
4,937,247	A	6/1990	King	
5,011,846	A	4/1991	Gittos et al.	
5,034,398	A	7/1991	King	
5,202,333	A	4/1993	Berger et al.	
5,240,954	A	8/1993	Tyers et al.	
5,272,137	A	12/1993	Blase et al.	
5,344,658	A	9/1994	Collin	
5,578,628	A	11/1996	Tyers et al.	
5,578,632	A	11/1996	Tyers et al.	
5,622,720	A	4/1997	Collin	
5,854,270	A	12/1998	Gambhir	
5,922,749	A	7/1999	Tyers et al.	
5,955,488	A	9/1999	Winterborn	
6,063,802	A	5/2000	Winterborn	
6,132,758	A	10/2000	Munayyer et al.	
6,284,749	B1	9/2001	Castillo et al.	
6,287,592	B1	9/2001	Dickinson	
6,294,548	B1	9/2001	James	
6,699,852	B2	3/2004	Robichaud	
7,109,339	B2	9/2006	Lee et al.	
7,947,724	B2	5/2011	Calderari et al.	
7,947,725	B2	5/2011	Calderari et al.	
7,960,424	B2	6/2011	Calderari et al.	
8,518,981	B2	8/2013	Calderari et al.	
2001/0020029	A1	9/2001	James	
2003/0095926	A1	5/2003	Dugger, III	
2004/0147510	A1 *	7/2004	Landau et al.	514/218

FOREIGN PATENT DOCUMENTS

EP	0 512 400 A1	4/1992
WO	WO-03100091	12/2003
WO	WO-2004045615	6/2004
WO	WO-2004067005	8/2004
WO	WO-2004703714	9/2004

OTHER PUBLICATIONS

CDER (Clinical Pharmacology and Biopharmaceutics Review (Sep. 2002).*

Perez et al. (cancer J. Sci Am. (1998) 4(1):52.*

R. M. Eglen et al., "Pharmacological characterization of RS 25259-197, a novel and selective 5-HT3 receptor antagonist, in vivo," Br. J Pharmacology 114:860-866 (1995).

Chelly, Jacques et al., Oral RS-25259 Prevents Postoperative Nausea and Vomiting Following Laparoscopic Surgery, Anesthesiology, 1996, vol. 85, No. 3A, p. A21.

Sorbe, Bengt, 5-HT-3 Receptor Antagonists as Antiemetic Agents in Cancer Chemotherapy, extracted from Expert Opinion on Investigational Drugs, 1996, vol. 5 No. 4, pp. 389-407.

Gaster, Laramie M. and King, Frank D., Serotonin 5-HT3 and 5-HT4 Receptor Antagonists, extracted from Medicinal Research Reviews, 1997 vol. 17, No. 2, pp. 163-214.

(Continued)

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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

(56) **References Cited**

OTHER PUBLICATIONS

Tang, Jun et al., "Efficacy of RS-25259, a Novel 5-HT3 Antagonist, in the Prevention of Postoperative Nausea and Vomiting after Major Gynecologic Surgery," Anesthesiology, 1997, vol. 85, No. 3 suppl. p. A329.

Tang, Jun et al., The Efficacy of RS-25259, a Long-Acting Selective 5-HT3 Receptor Antagonist, for Preventing Postoperative Nausea and Vomiting After Hysterectomy Procedures, Anesthesia and Analgesia, 1998, vol. 87, pp. 462-467.

Adis R&D Profile, Palonosetron RS 25259 197, Drugs in R&D, Oct. 1999, vol. 2, No. 4, pp. 251-252.

Piraccini Gaia et al., An Interesting 5-HT3 Receptor Antagonist Antiemetic for Patients Undergoing Chemotheraphy-based Conditioning Regimens, Blood, Nov. 16, 2001, vol. 98, No. 11, part 2, p. 350b, abstract No. 5169.

Stacher, Georg, Palonosetron Helsinn, Current Opinion in Investigational Drugs. Oct. 2002, vol. 3, No. 10, pp. 1502-1507.

Navari, Rudolph M., Pathogenesis-Based Treatment of Chemotherapy-Induced Nausea and Vomiting—Two New Agents, Journal of Supportive Oncology, 2003, vol. 1(2), pp. 89-103.

Chaitow, 1990, 3 pages.

Opposition Brief filed by Dr. Reddy's Laboratories (UK) Limited, opposition to European Patent No. 1601359 B1 dated Jul. 7, 2009.

Photolytic and oxidative degradation of an antiemetic agent, RG 12915 (Won C. M. et al., International Journal of Pharmaceutics 121. 95-105 (1995).

Palonosetron: a phase II dose ranging study to assess over a 7 day period the single dose pharmacokinetic profile of palonosetron in patients receiving highly emetogenic chemotherapy. Piraccini et al., Proc. Am. Soc. Clin. Oncol 2002 21 Abs 449 (2002).

Formulation and administration techniques to minimize injection pain and tissue damage associated with parenteral products. Larry A. Gatlin and Carol A. Brister Gatlin, from Injectable Drug Development: Techniques to Reduce Pain and Irritation (Edited by Pramod K. Gupta and Gayle A. Brazeau; published by Informa Health Care) 1999; ISBN 1574910957, 9781574910957, p. 401-421.

Parenteral Dosage Forms. Joanne Broadhead, from Part 11—Early drug development, pharmaceutical preformulation and formulation: a practice guide from candidate drug selection to commercial dosage form (Edited by Mark Gibson; Published by Interpharma Press, 2001; ISBN 1574911201, 9781574911206), p. 331-353.

Opposition Brief filed by Tecnimede Sociedade Tecnico-Medicinal S.A. in opposition to European Patent No. 1601359 B1, Jul. 8, 2009.

Response brief filed by Helsinn Healthcare S.A. dated Jul. 13, 2007, in response to the communication pursuant to Art. 96(2) EPC of Jan. 3, 2007 regarding Serial No. 04 706 657.6-2123.

European Patent Office official communication dated Jul. 19, 2006, regarding Serial No. 04 706 657.6.

Response of Helsinn Healthcare S.A. dated Nov. 29, 2006, regarding EPO official communication date Jul. 19, 2006.

Lachman et al., The Theory and Practice of Industrial Pharmacy, 1986, third edition, pp. 652-784.

Declaration of Valentino J. Stella, Ph.D. dated Sep. 19, 2007.

Opposition Brief filed by Martin Paul White, opposition to European Patent No. 1601359 B1, Jul. 8, 2009.

Wong et al. (1995), in British Journal of Pharmacology, vol. 114, pp. 851-859.

Cover page and pp. 642-644 and 783-784 of The Theory and Practice of Industrial Pharmacy, Third Edition, Lea and Febiger (1986).

Cover page and pp. 514-515 of Modern Pharmaceutics, Second Edition, Marcel Dekker (1990).

Cover page and pp. 142-143 of Pharmaceutical Dosage Forms: Parenteral Medications vol. 1, Second Edition, Marcel Dekker (1992).

Mitsuo Matsumoto et al., "Yakuzaigaku Manual", 1st edition, Nanzando Co., Ltd. (1989) 2 pages.

Michael J. Pikal, "Freeze Drying", Encyclopedia of Pharmaceutical Technology, Third Edition, Jan. 2007, pp. 1824-1825, vol. 3, Informa Pharmaceuticals and Healthcare.

Daniele Bonadeo, "Supplemental Declaration of Daniele Bonadeo Under 37 C.F.R. 1.132", filed in U.S. Appl. No. 11/388,270, Jun. 8, 2009.

Kranke et al., 2007 "Recent advances, trends, and economic considerations in . . . " Expert Opinion Pharmacotherp., 8(18): 3217-3235.

Morrow et al., 1995, "Progress in reducing nausea and emesis: Comparisons of ondansetron, granisetron, and tropisetron." Cancer, vol. 76, No. 3 pp. 343-357.

USPTO Notice of Allowance and Fees Due, U.S. Appl. No. 11/388,270, filed Mar. 24, 2006, Date Mailed Jan. 26, 2010.

USPTO Office Action, U.S. Appl. No. 11/129,839, Date Mailed Jan. 15, 2010.

Israili, Zafar H., "Clinical Pharmacology of Serotonin Receptor Type (5-HT3) Antagonists," Curr. Med. Chem. Central Nervous System Agents, 2001:1, 171-199.

Barton (Citrate Buffer Calculation) 2000, 2 pages.

USPTO Office Action, U.S. Appl. No. 11/201,035, Date Mailed Aug. 19, 2009.

Response of Helsinn Healthcare to opposition of EP Serial No. 04 706 657.6, dated Feb. 11, 2010.

Annex 1 (Statement of Walso Mossi, Ph.D.) to Response of Helsinn Healthcare to Opposition of EP Serial No. 04 706 657.6 dated Feb. 11, 2010.

Annex 2 to Response of Helsinn Healthcare to Opposition of EP Serial No. 04 706 657.6 dated Feb. 11, 2010.

Annex 3 to Response of Helsinn Healthcare to Opposition of EP Serial No. 04 706 657.6 dated Feb. 11, 2010.

Summary of Product Characteristics for Aloxi 250 (2009).

Scientific Discussion from the European Public Assessment Report for Aloxi (Palonoseteron Hydrochloride) 2006.

6th Edition, Handbook of Pharmaceutical Excipients (2009), pp. 247-250 (RPS Publishing).

Lewis, Gareth A (2006) 'Optimization Methods,' Encyclopedia of Pharmaceutical Technology, 1:1, 2452-2467.

May 24, 2011 Para. IV notice from Teva Pharmaceuticals re '724 and '725 patents.

May 24, 2011 Para. IV notice from Sandoz re '724 and '725 patents.

May 24, 2011 Para. IV notice from Dr. Reddy's re '724 and '725 patents.

Aug. 9, 2011 Para. IV notice from Dr. Reddy's re '424 patent.

Aug. 19, 2011 Para. IV notice from Teva Pharmaceuticals re '424 patent.

Sep. 22, 2011 Para. IV notice from Sandoz re '724, '725 and '424 patents.

Jul. 8, 2011 Complaint for patent infringement (D. N.J. case No. 11-03962).

Sep. 23, 2011 Complaint for patent infringement (D. N.J. case No. 11-5579).

Aug. 31, 2011 Answer and counterclaim of Dr. Reddy's Laboratories, Ltd. and Dr. Reddy's Laboratories, Inc. (D. N.J. case No. 11-03962).

Sep. 13, 2011 Sandoz Inc.'s answer to complaint for patent infringement and counterclaims (D. N.J. case No. 11-03962).

Sep. 13, 2011 Teva Pharmaceuticals USA, Inc. and Teva Pharmaceutical Industries Ltd.'s answer (D. N.J. case No. 11-03962).

Oct. 5, 2011 Plaintiff's reply to answer and counterclaim of Dr. Reddy's Laboratories, Ltd. and Dr. Reddy Laboratories, Inc. (D. N.J. case No. 11-03962).

Oct. 21, 2011 Plaintiffs reply to Sandoz Inc.'s answer to complaint for patent infringement and counterclaims (D. N.J. case No. 11-03962).

Oct. 24, 2011 Answer and counterclaim of Dr. Reddy's Laboratories, Ltd. and Dr. Reddy's Laboratories, Inc. (D. N.J. case No. 11-5579).

Oct. 24, 2011 Sandoz Inc.'s answer to complaint for patent infringement and counterclaims (D. N.J. case No. 11-5579).

Oct. 27, 2011 Order consolidating the two cases (D. N.J. case No. 11-5579).

Nov. 17, 2011 Plaintiffs' reply to answer and counterclaim of Dr. Reddy's Laboratories, Ltd. and Dr. Reddy's Laboratories, Inc. (D. N.J. case No. 11-03962).

Nov. 17, 2011 Plaintiffs' reply to Sandoz Inc.'s answer to complaint for patent infringement and counterclaims (D. N.J. case No. 11-03962).

(56) **References Cited**

OTHER PUBLICATIONS

Dec. 5, 2011 Teva Pharmaceuticals USA Inc. And Teva Pharmaceuticals Industries Ltd.'s answer to complaint for patent infringement of the '424 patent (D. N.J. case No. 11-03962).
May 21, 2012 Defendants' opening claim construction brief (including exhibits 1-31).
May 21, 2012 Plaintiffs' opening claim construction brief (including exhibits 1-15).
Jul. 20, 2012 Defendants' responsive claim construction brief (including exhibits 1-3).
Jul. 20, 2012 Plaintiffs' responsive claim construction brief (including Exhibits A and B).
Sep. 7, 2012 Court transcript from Sep. 7, 2012 Markman hearing and Plaintiffs' PowerPoint presentation (D. N.J. case No. 11-03962).
Dec. 1, 2011 Sandoz Inc.'s invalidity contentions pursuant to L. Pat. R. 3.6(c) (D. N.J. case No. 11-03962).
Dec. 1, 2011 Teva Pharmaceuticals USA, Inc. and Teva Pharmaceutical Industries, Ltd.'s invalidity contentions, pursuant to L. Pat. R. 3.6(c)(D. N.J. case No. 11-03962).
Dec. 1, 2011 Dr. Reddy's Laboratories, Ltd.'s and Dr. Reddy's Laboratories, Inc.'s invalidity contentions pursuant to L. Pat. R. 3.6(c) (D. N.J. case No. 11-03962).
Jan. 31, 2012 Plaintiff's responses to defendants' invalidity contentions (D. N.J. case No. 11-03962).
Sep. 25, 2012 Sandoz Inc.'s first amended invalidity contentions pursuant to L. Pat. R. 3.6(c) (D. N.J. case No. 11-03962).
Nov. 19, 2012 Plaintiffs' responses to Sandoz Inc.'s first amended invalidity contentions (D. N.J. case No. 11-03962).
L.G. Wade Jr., Organic Chemistry, Ch. 19: Amines, pp. 867-936 (Prentice Hall 3d ed. 1995).
L. Lachman et al., The Theory and Practice of Industrial Pharmacy, pp. 642-644, 783-784 (Lea & Febiger 3d ed. 1986).
P.P. DeLuca et al., Formulation of Small Volume Parenterals in Pharmaceutical Dosage Forms: Parenteral Medications, vol. 1, Ch. 5, pp. 173-248 (Avis, Lieberman, Lachman eds., Marcel Dekker Inc. 2d ed. 1992).
C.M. Won et al, Photolytic and Oxidative Degradation of an Antiemetic Agent, RGI2915, Int'l J Pharmaceutics 121:95-105 (1995).
R.D. Clark et al., 2-(Quinuciidin-3-yl)pyrido-[4,3-b]indol-l-ones and Isoquinoin-l-ones. Potent Conformationally Restricted 5-HT3 Receptor Antagonists, J Med. Chem. 36:2645-57 (1993).
L.A. Trissel, Drug Stability and Compatibility Issues, Handbook on Injectable Drugs, pp. XI-XVI (ASHP 7th ed. 1992).
J. Broadhead, Parenteral Dosage Forms, Pharmaceutical Preformulation and Formulation: A Practical Guide from Candidate Drug Selection to Commercial Dosage Form, Ch. 9, pp. 331-354 (Gibson ed., CRC Press 1st ed. 2001).
K.A. Connors et al., Chemical Stability of Pharmaceuticals: A Handbook for Pharmacists (John Wiley & Sons 2d ed. 1986).
ZOFRAN®, in The Physician's Desk Reference, op. 1503-07 (5th ed. 2001).
ANZEMET®, in The Physician's Desk Reference, pp. 680-683 (5th ed. 2001).
KYTRIL®, in The Physician's Desk Reference, pp. 3104-3106 (5th ed. 2001).
L.A. Trissel, Ondansetron HCI, in Handbook on Injectable Drugs, pp. 683-688 (ASHP 7th ed. 1992).
NAVOBAN® (tropisetron HCI) Malaysian Prescribing Information (Sep. 2000).
KYTRIL® (granisetron HCI) South African Prescribing Information (Dec. 1993).
S. Motola and S. Agharkar, Preformulation Research of Parenteral Medications, Pharmaceutical Dosage Forms: Parenteral Medications, vol. 1, Ch. 4, pp. 115-172 (Avis, Lieberman, Lachman eds., Marcel Dekker Inc. 2d ed. 1992).
J. Wells, Pharmaceutical Preformuatlion: The Physicochemical Properties of Drug Substances, Ch. 5: Drug Stability, pp. 152-191 (Ellis Horwod Ltd. 1988).
J. Swarbrick and Boylan, Encyclopedia of Pharmaceutical Technology, Excipients Chapter: Their Role in Parenteral Dosage Forms, vol. 19(2):137-172 (Marcel Dekker, Inc. 2000).
Handbook of Pharmaceutical Excipients, 3d Ed., (Kibbe ed. Pharmaceutical Press 2000); pp. 140-143, 191-194, 324-238.
G. Stacher, Palonosetron (Helsinn), Curro. Opin. Investig. Drugs, 3(10) 1502-7 (2002).
Handbook of Modern Pharmaceutical Analysis, (S. Ahuja et al. ed., Academic Press, 2001).
Jun. 8, 2009 Bonadeo Declaration.
Jun. 8, 2009 Bonadeo Declaration, Exhibit 2.
Jun. 8, 2009 Bonadeo Declaration, Exhibit 3.
HELSN0117262-69 (2008).
HELSN0117270-312 (2012).
Feb. 13, 2007 Statutory Declaration of Daniele Bonadeo, with Exhibit A.
Nov. 21, 2007 Statutory Declaration of Giorgio Calderari, Daniele Bonadeo, Roberta Cannella, Enrico Braglia, and Riccardo Braglia.
Reddy's Paragraph IV notice regarding all three patents (D. N.J. Case No. 12-2867), dated Mar. 30, 2012.
May 11, 2012 Complaint for patent infringement filed by Helsinn and Roche (D. N.J. Case No. 12-2867).
Jun. 26, 2012 Notice of Reddy's motion to dismiss (D. N.J. Case. No. 12-2867).
Jun. 26, 2012 Dr. Reddy's Laboratories, Ltd.'s and Dr. Reddy's Laboratories, Inc.'s memorandum of law in support of their motion to dismiss or for summary judgment of non-infringement of U.S. patent No. 7,947,724 (D. N.J. Case No. 12-2867) (including Exhibits 1-10).
Aug. 16, 2012 Notice of Plaintiffs' cross-motion for partial summary judgment of infringement (D. N.J. Case No. 12-2867).
Aug. 6, 2012 Plaintiffs' opposition to Defendants' motion to dismiss or for summary judgment of noninfringement and cross-motion for partial summary judgment of infringement (D. N.J. Case No. 12-1867) (including exhibits 1-4).
Schöneich declaration (D. N.J. Case No. 12-2867) (Including Exhibits A and 1-24), dated Aug. 6, 2012.
Sep. 4, 2012 Reddy's brief in opposition to Plaintiffs' cross-motion for partial summary judgment and reply memorandum of law in further support of Reddy's motion to dismiss or for summary judgment of non-infringement (D. N.J. Case No. 12-2867)(Including Exhibits 1-4).
DeLuca Declaration (D. N.J. Case No. Dec. 2867)(Including exhibits A-J), dated Sep. 3, 2012.
Sep. 10, 2012 Plaintiffs' letter to Judge Cooper in response to Reddy's combined opposition to Plaintiffs' cross-motion for partial summary judgment and reply in support of Reddy's motion to dismiss or for summary judgment of noninfringement (D. N.J. Case No. 12-2867)(including exhibits A and B).
Sep. 14, 2012 Dr. Reddy's letter in response to Plaintiffs' Sep. 10, 2012 letter (D. N.J. Case No. 12-2867).
USPTO Office Action, U.S. Appl. No. 11/388,268, filed Mar. 24, 2006, Mail Date Mar. 29, 2010.
USPTO Non-Final Office Action, U.S. Appl. No. 11/186,311, mailed Aug. 30, 2006.
USPTO Non-Final Office Action, U.S. Appl. No. 11/186,311, mailed Oct. 5, 2007.
USPTO Non-Final Office Action, U.S. Appl. No. 11/186,311, mailed Oct. 6, 2008.
USPTO Final Office Action, U.S. Appl. No. 11/186,311, mailed May 20, 2009.
USPTO Advisory Action, U.S. Appl. No. 11/186,311, mailed Jul. 15, 2009.
USPTO Notice of Allowance and Fees Due, U.S. Appl. No. 11/186,311, mailed Mar. 4, 2011.
USPTO Notice of Allowability, U.S. Appl. No. 11/186,311, dated May 24, 2011.
USPTO Non-Final Office Action, U.S. Appl. No. 11/388,268, mailed Jul. 17, 2006.
USPTO Non-Final Office Action, U.S. Appl. No. 11/388,268, mailed Nov. 17, 2006.
USPTO Non-Final Office Action, U.S. Appl. No. 11/388,268, mailed Oct. 3, 2007.

(56) **References Cited**

OTHER PUBLICATIONS

USPTO Non-Final Office Action, U.S. Appl. No. 11/388,268, mailed Mar. 26, 2008.
USPTO Final Office Action, U.S. Appl. No. 11/388,268, mailed Nov. 12, 2008.
USPTO Non-Final Office Action, U.S. Appl. No. 11/388,268, mailed Jul. 15, 2009.
USPTO Notice of Allowance and Fees Due, U.S. Appl. No. 11/388,268, mailed Dec. 22, 2010.
USPTO Non-Final Office Action, U.S. Appl. No. 11/388,269, mailed Jul. 19, 2006.
USPTO Non-Final Office Action, U.S. Appl. No. 11/388,269, mailed Nov. 17, 2006.
USPTO Non-Final Office Action, U.S. Appl. No. 11/388,269, mailed Sep. 20, 2007.
USPTO Non-Final Office Action, U.S. Appl. No. 11/388,269, mailed Jul. 9, 2008.
USPTO Interview Summary, U.S. Appl. No. 11/388,269, dated Apr. 28, 2009.
USPTO Final Office Action, U.S. Appl. No. 11/388,269, mailed May 20, 2009.
USPTO Advisory Action, U.S. Appl. No. 11/388,269, mailed Jul. 15, 2009.
USPTO Notice of Abandonment, U.S. Appl. No. 11/388,269, mailed Dec. 18, 2009.
USPTO Non-Final Office Action, U.S. Appl. No. 11/388,270, mailed Jul. 13, 2006.
USPTO Interview Summary, U.S. Appl. No. 11/388,270, dated Aug. 3, 2006.
USPTO Non-Final Office Action, U.S. Appl. No. 11/388,270, mailed Nov. 16, 2006.
USPTO Non-Final Office Action, U.S. Appl. No. 11/388,270, mailed Sep. 20, 2007.
USPTO Interview Summary, U.S. Appl. No. 11/388,270, dated Dec. 14, 2007.
USPTO Non-Final Office Action, U.S. Appl. No. 11/388,270, mailed Mar. 25, 2008.
USPTO Final Office Action, U.S. Appl. No. 11/388,270, mailed Oct. 29, 2008.
USPTO Advisory Action, U.S. Appl. No. 11/388,270, mailed Jan. 23, 2009.
USPTO Non-Final Office Action, U.S. Appl. No. 11/388,270, mailed Jul. 9, 2009.
USPTO Interview Summary, U.S. Appl. No. 11/388,270, dated Nov. 12, 2010.
USPTO Notice of Allowance and Fees Due, U.S. Appl. No. 11/388,270, mailed Jan. 5, 2011.
USPTO Non-Final Office Action, U.S. Appl. No. 13/087,012, mailed Mar. 12, 2012.
USPTO Non-Final Office Action, U.S. Appl. No. 13/087,012, mailed Jul. 19, 2012.
USPTO Interview Summary, U.S. Appl. No. 13/087,012, dated Feb. 15, 2013.
USPTO Notice of Allowance and Fees Due, U.S. Appl. No. 13/087,012, mailed Feb. 27, 2013.
USPTO Response to Amendment under Rule 312, U.S. Appl. No. 13/087,012, mailed Apr. 4, 2013.
USPTO Non-Final Office Action, U.S. Appl. No. 11/129,839, mailed Jun. 10, 2008.
Eisenberg et al. 2004, "Efficacy, safety and pharmacokinetics of palonosetron in patients receiving highly emetogenic cisplatin-based chemotherapy: a dose-ranging clinical study." Annals of Oncology, vol. 15, pp. 330-337.
Mayron et al. 1996, "Stability and compatibility of granistron hydrochloride in i.v. solutions and oral liquids and during simulated Y-site injection with selected drugs." Am J Health-Sys Pharm, 53: 294-304.
Trissel et al. 1997, "Compatibility of granisetron hydrochloride with selected drugs during simulated Y-site administration." Am J Health-Syst Pharm 54: 56-60.
USPTO Final Office Action, U.S. Appl. No. 11/129,839, mailed Mar. 17, 2009.
USPTO Advisory Action, U.S. Appl. No. 11/129,839, mailed Jul. 22, 2009.
USPTO Non-Final Office Action, U.S. Appl. No. 11/129,839, mailed Jan. 15, 2010.
USPTO Examiner Interview Summary, U.S. Appl. No. 11/129,839, mailed Nov. 9, 2010.
USPTO Notice of Allowance and Fees Due, U.S. Appl. No. 11/129,839, mailed Jan. 3, 2011.
USPTO Notice of Abandonment, U.S. Appl. No. 11/129,839, mailed Apr. 18, 2011.
USPTO Non-Final Office Action, U.S. Appl. No. 13/077,374, mailed Feb. 17, 2012.
Roila et al. 1998, "Prevention of chemotherapy- and radiotherapy-induced emesis: Results of the Perugia consensus conference." Annals of Oncology, vol. 9, pp. 811-819.
USPTO Final Office Action, U.S. Appl. No. 13/077,374, mailed Nov. 23, 2012.
Piraccini, Gaia et al., American Society of Clinical Oncology May 12-15, 2001 San Francisco—USA (vol. 20, part 1 of 2, 2001) (Abstract No. 1595).
USPTO Non-Final Office Action, U.S. Appl. No. 11/201,035, mailed May 16, 2008.
USPTO Final Office Action, U.S. Appl. No. 11/201,035, mailed Feb. 4, 2009.
USPTO Final Office Action, U.S. Appl. No. 11/201,035, mailed Jun. 8, 2010.
FDA approval letter of Aloxi (palonosetron hydrochloride injection), dated Jul. 25, 2003.
Macciocchi A, Chernoff SB, Gallagher SC. A phase II dose-ranging study to assess intravenous doses of palonosetron for the prevention of highly emetogenic chemotherapy-induced nausea and vomiting. In: Program/Proceedings of the 38th Annual Meeting of the American Society of Clinical Oncology; May 18-21, 2002; Orlando, Fla. Abstract 1480.
Grunberg SM, Hajdenberg J, Charu V, et al. Palonosetron is active in preventing acute and delayed emesis following moderately emetogenic chemotherapy: results of a phase III trial. Support Care Cancer 2002;10:Abstract P-113.
Aapro MS, Selak E, Lichinitser M, et al. Palonosetron is more effective than ondansetron in preventing chemotherapy-induced nausea and vomiting in patients receiving moderately emetogenic chemotherapy: results of a phase III trial. In: Program/Proceedings of the 39th Annual Meeting of the American Society of Clinical Oncology; May 31-Jun. 3, 2003; Chicago, Ill. Abstract 2918.
Aapro MS, Bertoli L, Lordick F, et al. Palonosetron is effective in preventing acute and delayed chemotherapy induced nausea and vomiting in patients receiving highly emetogenic chemotherapy. 15th MASCC International Symposium, Berlin, Germany. Support Care Cancer, vol. 11, No. 6, Jun. 2003, A17.
Cartmell AD, Ferguson S, Yanagihara R, et al. Protection against chemotherapy-induced nausea and vomiting is maintained over multiple cycles of moderately or highly emetogenic chemotherapy by palonosetron, a potent 5 HT3 receptor antagonist. In: Program/Proceedings of the 39th Annual Meeting of the American Society of Clinical Oncology; May 31-Jun. 3, 2003; Chicago, Ill. Abstract 3041.
Sabra, Choice of a 5-HT3 Receptor Antagonist for the Hospital Formulary, EHP, Oct. 1996, vol. 2, Supp 1, S19-S24.
Gregory and Ettinger, 5HT3 receptor antagonists for the prevention of chemotherapy-induced nausea and vomiting. A comparison of their pharmacology and clinical efficacy. Drugs, Feb. 1998; 55(2): 173-189.
Full Prescribing Information for Aloxi (palonosetron HCI) injection for Intravenous Use (2008).
Drug, Dose & Schedule Recommendations for Antiemetic Regimens (American Society for Clinical Oncology) (2006).
Yamakuni, et al., The Journal of Pharmacology and Experimental Therapeutics, Probable Involvement of the 5-Hydroxytryptamine4 Receptor in Methotrexate-Induced Delayed Emesis in Dogs, 2000, The American Society for Pharmacology and Experimental Therapeutics, vol. 292, No. 3, p. 1002-1294.

(56) **References Cited**

OTHER PUBLICATIONS

Geling, et al., Should 5-Hydroxytryptamine-3 Receptor Antagonists Be Administered Beyond 24 Hours After Chemotherapy to Prevent Delayed Emesis? Systematic Re-Evaluation of Clinical Evidence and Drug Cost Implications, Journal of Clinical Oncology, vol. 23, No. 6, Feb. 20, 2005 (American Society of Clinical Oncology), pp. 1289-1294.

Rojas, et al., International Anesthesia Research Society, Palonosetron Exhibits Unique Molecular Interactions with 5-HT3 Receptor, vol. 107, No. 2, Aug. 2008, p. 469-478.

Rojas, et al., Palonosetron triggers 5-HT3 receptor internalization and causes inhibition of receptor function, European Journal of Pharmacology 626 (2010), p. 193-199.

Regan-Shaw, et al., Dose translation from animal to human studies revisited, The FASEB Journal, Life Sciences Forum, p. 659-661.

Saito, et al., Palonosetron plus dexamethasone versus granisetron plus dexamethasone for prevention of anusea and vomiting during chemotherapy: a double-blind, double-dummy, randomised, comparative phased III trial, www.thelancet.com/oncology, vol. 10, Feb. 2009, p. 115-124.

Palonosetron: more than just another option?. www.thelancet.com/oncology, vol. 10, Feb. 2009, p. 100-101.

Lorusso, et al., Single dose of palonosetron plus dexamethasone to control nausea, vomiting and to warrant an adequate food intake in patients treated with highly emetogenic chemotherapy (HEC). Preliminary results, Support Care Cancer, published online Mar. 18, 2009.

Grunberg, et al., Effectiveness of a single-day three-drug regimen of dexamethasone, palonosetron, and aprepitant for the prevention of acute and delayed nausea and vomiting caused by moderately emetogenic chemotherapy, Support Care Cancer (2009) 17:589-594.

Celio, et al., Clinical update on palonosetron in the management of chemotherapy-induced nausea and vomiting, Tumor, 94: 447-452, 2008.

Ellebaek, et al., Optimizing antiemetic therapy in multiple-day and multiple cycles of chemotherapy, Lippincott williams & Wilkins, Current Opinion in Supportive and Palliative Care, 2008, 2:28-34.

Herrington, et al., Randomized, Placebo-controlled, Pilot Study Evaluating Aprepitant Single Dose Plus Palonosetron and Dexamethasone for the Prevention of Acute and Delayed Chemotherapy-induced Nausea and Vomiting, American Cancer Society, published online Mar. 7, 2008 in Wiley InterScience (www.interscience.wiley.com).

Massa, et al., Palonosetron plus dexamethasone effectively prevents acute and delayed chemotherapy-induced nausea and vomiting following highly or moderately emetogenic chemotherapy in pretreated patients who have failed to respond to a previous antiemetic treatment: Comparison between elderly and non-elderly patient response, Critical Reviews in Oncology/Hematology 70 (2009) 83-91.

2006 Update of the ASCO Recommendations for Antiemetics in Oncology: Guideline Summary, American Cancer Society of Clinical Oncology, Jul. 2006, www.jopasco.org.

Warr, David, Standard treatment of chemotherapy-induced emesis, Support Care Cancer, vol. 5, pp. 12-16, 1997.

Aapro, M.S., et al. A phase III, double-blind, randomized trial of palonosetron compared with ondansetron in preventing chemotherapy-induced nausea and vomiting following highly emetogenic chemotherapy. Annals of Oncology, vol. 17, pp. 1441-1449, 2006.

Eisenberg, Peter, et al. Improved Prevention of Moderately Emetogenic Chemotherapy-Induced Nausea and Vomiting with Palonosetron, a Pharmacologically Novel5-HT3 Receptor Antagonist. Cancer, vol. 98, No. 11, pp. 2473-2482, Dec. 1, 2003.

Gandara, D.R., et al. The delayed-emesis syndrome from cisplatin: Phase III evaluation of ondansetron versus placebo. Semin Oneal vol. 19, No. 4, pp. 67-71, Aug. 1992 (suppl 10).

Goedhals, L., et al. Control of delayed nausea and vomiting with granisetron plus dexamethasone or dexamethasone alone in patients receiving highly emetogenic chemotherapy: A double-blind, placebo-controlled, comparative study. Ann Oneal, vol. 9, pp. 661-666, 1998.

Gralla, R., et al. Palonosetron improves prevention of chemotherapy-induced nausea and vomiting following moderately emetogenic chemotherapy: results of a double-blind randomized phase III trial comparing single doses of palonosetron with ondansetron. Annals of Oncology, vol. 14, pp. 1570-1577, 2003.

Italian Group for Antiemetic Research. Dexamethasone alone or in combination with ondansetron for the prevention of delayed nausea and vomiting induced by chemotherapy. N Engl J Med, vol. 342, No. 21, pp. 1554-1559, May 25, 2000.

Kaizer, L., et al. Effect of schedule and maintenance on the antiemetic efficacy of ondansetron combined with dexamethasone in acute and delayed nausea and emesis in patients receiving moderately emetogenic chemotherapy: A phase III trial by the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol, vol. 12, No. 5, pp. 1050-1057, May 1994.

Latreille, J., et al. Use of dexamethasone and granisetron in the control of delayed emesis for patients who receive highly emetogenic chemotherapy: National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol, vol. 16, No. 3, pp. 1174-1178, Mar. 1998.

Antiemetic Subcommittee of the Multinational Association of Supportive Care in Cancer (MCSCC). Prevention of chemotherapy- and radiotherapy-induced emesis: Results of the Perugia Consensus Conference. Annals of Oncology, vol. 9, pp. 811-819, 1998.

Moyer, Paula. New Understanding of Emesis Pathways Leading to New Treatment, Better Control. Oncology Times, vol. 25, Issue 10, pp. 48-51, May 25, 2003.

Navari, R.M., et al. Oral ondansetron for the control of cisplatin-induced delayed emesis: A large, multicenter, double-blind, randomized comparative trial of ondansetron versus placebo. J Clin Oncol,vol. 13, No. 9, pp. 2408-2416, Sep. 1995.

Olver, I., et al. A multicenter, double-blind study comparing placebo, ondansetron and ondansetron plus dexamethasone for the control of cisplatin-induced delayed emesis. Ann Oncol, vol. 7, pp. 945-952, 1996.

Pater, J.L., et al. The role of the 5-HT3 antagonists ondansetron and dolasetron in the control of delayed onset nausea and vomiting in patients receiving moderately emetogenic chemotherapy. Ann Oncol, vol. 8, pp. 181-185, 1997.

Rojas, Camilo, et al. The Antiemetic 5-HT3 Receptor Antagonist Palonosetron Inhibits Substance P-Mediated Responses In Vitro and In Vivo. J Pharmacal Exper Thera, vol. 335, No. 2, pp. 362-368, 2010.

Sorbe, B. G., et al. A study evaluating the efficacy and tolerability of tropisetron in combination with dexamethasone in the prevention of delayed platinum-induced nausea and emesis. Cancer, vol. 83, pp. 1022-1032, 1998.

Stewart, A., et al. Ondansetron Compared with Granisetron in the Prophylaxis of Cyclophosphamide-Induced Emesis in Out-Patients: A Multicentre, Double-Blind, Double-Dummy, Randomised, Parallel-Group Study. Oncology, vol. 52, pp. 202-210, 1995.

Weiderpass, Elisabete, et al. Use of an NK1 Receptor Antagonist to Prevent Delayed Emesis After Cisplatin. Journal of the National Cancer Institute, vol. 89, No. 11, pp. 817-818, Jun. 4, 1997.

Akers, Michael J., Excipient-Drug Interactions in Parenteral Formulations. Journal of Pharmaceutical Sciences, vol. 91, No. 11, Nov. 2002, pp. 2283-2300.

Maemondo, et al., A phase II study of palonosetron combined with dexamethasone to prevent nausea and vomiting induced by highly emetogenic chemotherapy. Annals of Oncology, Nov. 2009, vol. 20, No. II, pp. 1860-1866.

Program/Proceedings American Society of Clinical Oncology, vol. 20, Part 1 of 2, 2001, Abstract No. 1595 and associated poster presentation.

Saito, et al., Review of palonosetron: emerging data distinguishing it as a novel 5-HT3 receptor antagonist for chemotherapy-induced nausea and vomiting. Expert Opin. Pharmacother (2010) II (6), pp. 1003-1014.

MGI-HHC_SEC_filing (2001).

ROCHE0008749-876 (1995) (portions redacted).

HELSN0135068-82 (1998) (portions redacted).

(56) **References Cited**

OTHER PUBLICATIONS

English-language translation of Italian-language portions of HELSN0135068-82 (1998).
HELSN0161327-348 (2000) (portions redacted).
HELSN0138407-24 (1998) (portions redacted).
HELSN0376401-469 (2002) (portions redacted).
HELSN0392650-72 (1999) (portions redacted).
Dr. Reddy's Labs., Ltd.'s and Dr. Reddy's Labs., Inc.'s Memorandum of Law in Support of Their Motion to Amend Their Invalidity Contentions dated Feb. 15, 2013 (D.N.J. Case No. 11-3962).
HELSN0376719-21 (2001).
HELSN0376722-23 (2001).
HELSN0376724 (2002).
Dr. Reddy's Laboratories, Ltd.'s and Dr. Reddy's Laboratories, Inc.'s Redline of Proposed Amended Invalidity Contentions Pursuant to L. Pat. R. 3.6(c) filed Feb. 15, 2013 (D.N.J. Case No. 11-3962).
Dr. Reddy's Laboratories, Ltd.'s and Dr. Reddy's Laboratories, Inc.'s Reply Memorandum of Law in Further Support of Their Motion to Amend Their Invalidity Contentions dated Mar. 15, 2013 (D.N.J. Case No. 11-3962).
Teva Pharm. Indus., Ltd.'s and Teva Pharm. USA, Inc.'s Memorandum in Support of Their Motion to Amend Invalidity Contentions dated Feb. 15, 2013 (D.N.J. Case No. 1-3962).
HELSN0388553-65 (1998) (portions redacted).
HELSN0388566-68 (1998) (portions redacted).
HELSN0388569-74 (1998) (portions redacted).
HELSN0388587-91 (1998) (portions redacted).
HELSN0388592-95 (1998) (portions redacted).
English-language translation of HELSN0388592-95 (1998) (portions redacted).
HELSN0388596-97 (1998) (portions redacted).
HELSN0388604 (1998) (portions redacted).
HELSN0388605-06 (1998) (portions redacted).
HELSN0388607-09 (1998) (portions redacted).
HELSN0389134 44 (1999) (portions redacted).
HELSN0389145-48 (1999) (portions redacted).
HELSN0389149-61 (2000) (portions redacted).
HELSN0392047-48 (1998) (portions redacted).
HELSN0392393-94 (1998) (portions redacted).
HELS0393657-61 (2000) (portions redacted).
English-language translation of Italian-language portions of HELSN039657-61 (2000) (portions redacted).
Excerpts from Calderari Deposition Transcript, pp. 1-4, 229-232, and 278-393 (2013) (portions redacted).
HELSN0000093-9 (2006) (portions redacted).
HELSN0004207 (2002).
HELSN0004217 (2002).
Teva Pharm. Indus., Ltd.'s and Teva Pharm. USA, Inc.'s Reply in Support of Their Motion to Amend Their Invalidity Contentions dated Mar. 15, 2013 (D.N.J. Case No. 1-3962).
HELSN00388448-542 (1998-1999) (portions redacted).
English-language translation of Italian-language portions of HELSN00388448-542 (1998-1999) (portions redacted).
HELSN0388543-44 (1999) (portions redacted).
HELSN0388545-52 (1998) (portions redacted).
HELSN0388575-76 (1998) (portions redacted).
HELSN0388577-80 (1998) (portions redacted).
HELSN0388581-82 (1998) (portions redacted).
HELSN0388583-84 (1998) (portions redacted).
HELSN0388585 (1998) (portions redacted).
HELSN0388586 (1998) (portions redacted).
HELSN0388598-601 (1998) (portions redacted).
HELSN0388602-03 (1998) (portions redacted).
HELSN0388610 (1998) (portions redacted).
Sandoz Inc.'s Redacted Memorandum of Law in Support of its Motion to Amend its Invalidity Contentions dated Feb. 15, 2013 (D.N.J. Case No. 11-3962).
Exhibit G to Sandoz Inc.'s Redacted Memorandum of Law in Support of its Motion to Amend its Invalidity Contentions dated Feb. 15, 2013 (D.N.J. Case No. 11-3962).
Sandoz Inc.'s Redacted Reply Memorandum of Law in Support of its Motion to Amend its Invalidity Contentions dated Mar. 15, 2013 (D.N.J. Case No. 11-3962).
Aurobindo Pharma Ltd. Paragraph IV notice regarding U.S. Patent Nos. 7,947,724; 7,947,725; and 7,960,424, dated Mar. 5, 2013 (D. Del. Case No. 13-688).
Complaint for patent infringement filed by Helsinn Healthcare S.A. and Roche Palo Alto LLC against Aurobindo Pharma Ltd. And Aurobindo Pharma USA Inc. dated Apr. 16, 2013 (D. Del. Case No. 13-688).
Accord Healthcare, Inc. Paragraph IV notice regarding U.S. Patent Nos. 7,947,724; 7,947,725; and 7,960,424, dated Apr. 3, 2013.
Drug Marketing Approval Document for Aloxi I.V. Drip Infusion Bag 0 75 mg, Japanese Ministry of Health, Labour and Welfare (2012).
English-language translation of Cite No. 800 (2012).
Approval of Partial Changes in Drug Marketing Approved Items for Aloxi I.V. Drip Infusion Bag 0.75 mg, Japanese Ministry of Health, Labour and Welfare (2012).
English-language translation of Cite No. 802 (2012).
USPTO Notice of Allowance and Fees Due, U.S. Appl. No. 13/087,012, mailed Jul. 3, 2013.
USPTO Non-Final Office Action and Examiner-Initiated Interview Summary, U.S. Appl. No. 13/901,437, mailed Jul. 29, 2013.
USPTO Interview Summary, U.S. Appl. No. 13/087,012 dated Jun. 13, 2013.
USPTO Notice of Allowance and Fees Due and Examiner-Initiated Interview Summary, U.S. Appl. No. 13/901,288, mailed Sep. 6, 2013.
Feb. 9, 2009 Bonadeo Declaration.
Bedford Laboratories Paragraph IV Letter dated Aug. 13, 2013.
Defendants Aurobindo Pharma Ltd.'s and Aurobindo Pharma USA Inc.'s Answer, Affirmative Defenses, and Counterclaims, dated Aug. 23, 2013 (D. Del. Case No. 13-688).
Plaintiff's Answer to the Counterclaims of Aurobindo Pharma USA Inc. and Aurobindo Pharma Ltd., dated Sep. 13, 2013 (D. Del. Case No. 13-688).
Aurobindo Pharma Ltd. Paragraph IV notice regarding U.S. Patent No. 8,518,981, dated Sep. 19, 2013.
Dr. Reddy's Laboratories, Ltd.'s and Dr. Reddy's Laboratories, Inc.'s Amended Invalidity Contentions Pursuant to L. Pat. R. 3.6(c), dated Jul. 8, 2013 (D.N.J. Case Nos. 11-3962 and 11-5579; consolidated).
Plaintiffs' Responses to Dr. Reddy's Laboratories, Ltd. And Dr. Reddy's Laboratories, Inc.'s Amended Invalidity Contentions, dated Aug. 19, 2013 (D.N.J. Case Nos. 11-3962 and 11-5579; consolidated) (confidentiality designation redacted).
Sandoz Inc.'s Second Amended Invalidity Contentions Pursuant to L. Pat. R. 3.7, dated Jul. 5, 2013 (D.N.J. Case Nos. 11-3962 and 11-5579; consolidated) (confidentiality designation and other portions redacted).
Plaintiffs' Responses to Sandoz Inc.'s Second Amended Invalidity Contentions, dated Aug. 19, 2013 (D.N.J. Case Nos. 11-3962 and 11-579; consolidated) (confidentiality designation and other portions redacted).
Defendants Teva Pharmaceuticals USA, Inc. and Teva Pharmaceutical Industries, Ltd.'s First Amended Invalidity Contentions Pursuant to L. Pat. R. 3.6(c), dated Jul. 5, 2013 (D.N.J. Case Nos. 11-3962 and 11-5579; consolidated) (confidentiality designation redacted).
Plaintiffs' Responses to Teva Pharmaceuticals USA, Inc. and Teva Pharmaceutical Industries, Ltd.'s First Amended Invalidity Contentions, dated Aug. 19, 2013 (D.N.J. Case Nos. 11-3962 and 11-5579; consolidated) (confidentiality designation redacted).
Opening Expert Report of Dr. Bert Spilker, dated Sep. 9, 2013 (D.N.J. Case Nos. 11-3962 and 11-5579; consolidated) (confidentiality designation and other portions redacted).
Expert Report of David G. Frame, Pharm.D., dated Sep. 5, 2013 (D.N.J. Case Nos. 11-3962 and 11-5579; consolidated) (confidentiality designation and other portions redacted).
Expert Report of Lee Kirsch, Ph.D., dated Sep. 9, 2013 (D.N.J. Case Nos. 11-3962 and 11-5579; consolidated) (confidentiality designation and other portions redacted).
Expert Report of Patrick P. DeLuca, Ph.D., dated Sep. 9, 2013 (D.N.J. Case Nos. 11-3962 and 11-5579; consolidated) (confidentiality designation and other portions redacted).

(56) **References Cited**

OTHER PUBLICATIONS

Expert Report of Paul Myrdal, Ph.D., dated Sep. 9, 2013 (D.N.J. Case Nos. 11-3962 and 11-5579; consolidated) (confidentiality designation and other portions redacted).
Complaint for patent infringement filed by Helsinn Healthcare S.A. and Roche Palo Alto LLC against Ben Venue Laboratories, Inc. d/b/a Bedford Laboratories regarding U.S. Patent Nos. 7,947,724, 7,947,725, 7,960,424, and 8,518,981 dated Sep. 25, 2013 (D. Del. Case No. 13-1612).
Complaint for patent infringement filed by Helsinn Healthcare S.A. and Roche Palo Alto LLC against Dr. Reddy's Laboratories, Ltd., Dr. Reddy's Laboratories, Inc., Sandoz Inc., Teva Pharmaceuticals USA, Inc., and Teva Pharmaceutical Industries, Ltd. regarding U.S. Patent No. 8,518,981 dated Sep. 30, 2013 (D.N.J. Case No. (13-5815)).
Aurobindo Pharma Ltd. Paragraph IV Letter regarding U.S. Patent Nos. 8,598,218 and 8,598,219 dated Jan. 21, 2014 (portions redacted).
Sandoz Inc. Paragraph IV Letter regarding U.S. Patent Nos. 8,598,218 and 8,598,219 dated Feb. 3, 2014 (portions redacted).
Bedford Laboratories division of Ben Venue Laboratories, Inc. Paragraph IV Letter regarding U.S. Patent Nos. 8,598,218 and 8,598,219 dated Feb. 6, 2014 (portions redacted).
Defendants Aurobindo Pharma Ltd.'s and Auromedics Pharma LLC's Amended Answer, Affirmative Defenses, and Counterclaims regarding U.S. Patent Nos. 7,947,724, 7,947,725, 7,960,424, 8,518,981, 8,598,218, and 8,598,219, dated Feb. 11, 2014 (D. Del. Case No. 13-688).
Ben Venue Laboratories, Inc.'s Answer and Counterclaims to Amended Complaint regarding U.S. Patent Nos. 7,947,724, 7,947,725, 7,960,424, 8,518,981, 8,598,218, and 8,598,219, dated Feb. 24, 2014 (D. Del. Case No. 13/1612).
Cipla Limited Paragraph IV Letter regarding U.S. Patent Nos. 7,947,724, 7,947,725, 7,960,424, 8,518,981, 8,598,218, and 8,598,219 dated Feb. 24, 2014 (portions redacted).
Dr. Reddy's Laboratories, Ltd.'s and Dr. Reddy's Laboratories, Inc.'s Invalidity Contentions regarding U.S. Patent Nos. 8,518,981, 8,598,218, and 8,598,219 dated Mar. 17, 2014 (D.N.J. Case No. 13/5815) (confidentiality designation and other portions redacted).
Sandoz Inc.'s Invalidity Contentions Pursuant to L. Pat. R. 3.3 and 3.6(c) regarding U.S. Patent Nos. 8,518,981, 8,598,218, and 8,598,219 dated Mar. 17, 2014 (D.N.J. Case No. 13/5815) (confidentiality designation and other portions redacted).
Teva Pharmaceuticals USA, Inc. and Teva Pharmaceutical Industries Ltd.'s Invalidity Contentions Pursuant to L. Pat. R. 3.6(c) regarding U.S. Patent Nos. 8,518,981, 8,598,218, and 8,598,219 dated Mar. 17, 2014 (D.N.J. Case No. 13/5815) (confidentiality designation and other portions redacted).

* cited by examiner

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_3 (5-hydroxytryptamine) receptor antagonists has been developed that treat such emesis by antagonizing cerebral functions associated with the 5-HT_3 receptor. See *Drugs Acting on 5-Hydroxytryptamine Receptors*: The Lancet Sep. 23, 1989 and references cited therein. Drugs within this class include ondansetron, granisetron, alosetron, tropisetron, and dolasetron. These 5-HT_3 antagonists are often administered intravenously shortly before chemotherapy or radiotherapy is initiated, and can be administered more than once during a cycle of chemotherapy or radiotherapy. In addition, they are often supplied as tablets or oral elixirs to either supplement an intravenous administration, or to ease home usage of the drug if the patient is self-administering the chemotherapeutic regimen.

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

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

Ingredient	Mg
Palonosetron 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 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® (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_3 receptor antagonist and its pharmaceutically acceptable carriers that would facilitate making a formulation with this increased stability.

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

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

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

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

SUMMARY OF THE INVENTION

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

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

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

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

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

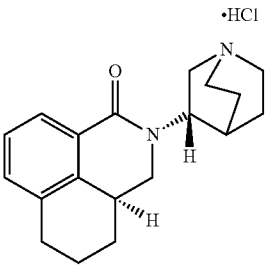
DETAILED DESCRIPTION OF THE INVENTION

Definitions

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

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

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



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

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

"Pharmaceutically acceptable salts" means salts which are pharmaceutically acceptable, as defined above, and which possess the desired pharmacological activity. Such salts include acid addition salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or with organic acids such as acetic acid, propionic acid, hexanoic acid, heptanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, o-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2,-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid p-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, p-toluenesulfonic acid, camphorsulfonicacid, 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 preferably is about 10 to 30 seconds. In one particular embodiment the palonosetron is supplied in vials that comprise 5 ml. of solution, which equates to about 0.25 mg of palonosetron at a concentration of about 0.05 mg/ml.

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

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

- The formulation may comprise palonosetron or a pharmaceutically acceptable salt thereof in a concentration from about 0.02 mg/mL to about 1.0 mg/mL, from about 0.03 mg/mL to about 0.2 mg/mL palonosetron hydrochloride, and most optimally about 0.05 mg/ml.
- The formulation may comprise citrate buffer in a concentration of from about 10 to about 40 millimoles, or 15-30 millimoles.
- The formulation may comprise EDTA in a concentration of from about 0.005 mg/ml to about 1.0 mg/ml, or about 0.3 to about 0.7 mg/ml, and most optimally about 0.5 mg/ml.

The inventors have further discovered that the addition of mannitol and a chelating agent can increase the stability of palonosetron formulations. Therefore, in still another embodiment the invention provides a pharmaceutically stable solution for preventing or reducing emesis comprising a) palonosetron or a pharmaceutically acceptable salt thereof and b) a pharmaceutically acceptable carrier, wherein the pharmaceutically acceptable carrier comprises a chelating agent and mannitol. Similarly, in another embodiment the invention provides a method of formulating a pharmaceutically stable solution of palonosetron comprising admixing a) palonosetron or a pharmaceutically acceptable salt thereof and b) a pharmaceutically acceptable carrier, wherein the pharmaceutically acceptable carrier comprises a chelating agent and mannitol. The chelating agent is preferably EDTA, and, in various embodiments the chelating agent is present in a concentration of from about 0.005 to about 1.0 mg/mL or from about 0.05 mg/mL to about 1.0 mg/mL or from about 0.3 to about 0.7 mg/ml, or most optimally about 0.5 mg/mL. In various embodiments the mannitol is present in a concentration of from about 10.0 mg/ml to about 80.0 mg/ml, from about 20.0 mg/mL to about 60.0 mg/ml, or from about 40.0 to about 45.0 mg/ml.

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

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

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

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

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

EXAMPLES

Example 1

Stabilizing pH

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

Example 2

Stabilizing Concentration Ranges

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

Example 3

Tonicifying Agent

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

Example 4

Formulation I

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

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

*calculated as a free base

Example 5

Formulation II

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

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

*calculated as a free base

Example 6

Stability of Palonosetron without Dexamethasone

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

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

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

Example 7

Stability of Palonosetron with Dexamethasone

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

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

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

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

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[a)]
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[b)] plus rubber stopper[c)]

[a)]Calculated based on the weight of free base.
[b)]Polyethylene multilayer film infusion bag.
[c)]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;
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.

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±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±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;

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.

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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.

(51) **Int. Cl.**

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A61K 47/12	(2006.01)
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USPC 514/296, 397

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,695,578	A	9/1987	Coates et al.
4,753,789	A	6/1988	Tyers et al.
4,886,808	A	12/1989	King
4,906,755	A	3/1990	Gittos
4,929,632	A	5/1990	Tyers et al.
4,937,247	A	6/1990	King
5,011,846	A	4/1991	Gittos et al.
5,034,398	A	7/1991	King
5,202,333	A	4/1993	Berger et al.
5,240,954	A	8/1993	Tyers et al.
5,272,137	A	12/1993	Blase et al.
5,344,658	A	9/1994	Collin
5,578,628	A	11/1996	Tyers et al.
5,578,632	A	11/1996	Tyers et al.
5,622,720	A	4/1997	Collin
5,854,270	A	12/1998	Gambhir
5,922,749	A	7/1999	Tyers et al.
5,955,488	A	9/1999	Winterborn
6,063,802	A	5/2000	Winterborn
6,132,758	A	10/2000	Munayyer et al.
6,284,749	B1	9/2001	Castillo et al.
6,287,592	B1	9/2001	Dickinson
6,294,548	B1	9/2001	James
6,699,852	B2	3/2004	Robichaud
7,109,339	B2	9/2006	Lee et al.
7,947,724	B2	5/2011	Calderari et al.
7,947,725	B2	5/2011	Calderari et al.
7,960,424	B2	6/2011	Calderari et al.
8,518,981	B2	8/2013	Calderari et al.
8,598,218	B2	12/2013	Calderari et al.

(Continued)

FOREIGN PATENT DOCUMENTS

EP	0 512 400 A1	4/1992
WO	WO-03100091	12/2003

(Continued)

OTHER PUBLICATIONS

Perez et al. (cancer J. Sci Am. (1998) 4_1):52.*

R. M. Eglen et al., "Pharmacological characterization of RS 25259-197, a novel and selective 5-HT3 receptor antagonist, in vivo," Br. J Pharmacology 114:860-866 (1995).

Chelly, Jacques et al., Oral RS-25259 Prevents Postoperative Nausea and Vomiting Following Laparoscopic Surgery, Anesthesiology, 1996, vol. 85, No. 3A, p. A21.

Sorbe, Bengt, 5-HT-3 Receptor Antagonists as Antiemetic Agents in Cancer Chemotherapy, extracted from Expert Opinion on Investigational Drugs, 1996, vol. 5 No. 4, pp. 389-407.

Gaster, Laramie M. and King, Frank D., Serotonin 5-HT3 and 5-HT4 Receptor Antagonists, extracted from Medicinal Research Reviews, 1997 vol. 17, No. 2, pp. 163-214.

Tang, Jun et al., "Efficacy of RS-25259, a Novel 5-HT3 Antagonist, In the Prevention of Postoperative Nausea and Vomiting after Major Gynecologic Surgery," Anesthesiology, 1997, vol. 85, No. 3 suppl. p. A329.

(Continued)

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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

(56) **References Cited**

U.S. PATENT DOCUMENTS

8,598,219	B2	12/2013	Calderari et al.	
2001/0020029	A1	9/2001	James	
2003/0095926	A1	5/2003	Dugger, III	
2004/0147510	A1 *	7/2004	Landau et al.	514/218
2013/0261149	A1	10/2013	Calderari et al.	
2013/0261150	A1	10/2013	Calderari et al.	
2013/0289065	A1	10/2013	Calderari et al.	
2014/0039000	A1	2/2014	Calderari et al.	

FOREIGN PATENT DOCUMENTS

WO	WO-2004045615	6/2004
WO	WO-2004067005	8/2004
WO	WO-2004703714	9/2004

OTHER PUBLICATIONS

Tang, Jun et al., The Efficacy of RS-25259, a Long-Acting Selective 5-HT3 Receptor Antagonist, for Preventing Postoperative Nausea and Vomiting After Hysterectomy Procedures, Anesthesia and Analgesia, 1998, vol. 87, pp. 462-467.

Adis R&D Profile, Palonosetron RS 25259 197, Drugs in R&D, Oct. 1999, vol. 2, No. 4, pp. 251-252.

Piraccini Gaia et al., An Interesting 5-HT3 Receptor Antagonist Antiemetic for Patients Undergoing Chemotheraphy-based Conditioning Regimens, Blood, Nov. 16, 2001, vol. 98, No. 11, part 2, p. 350b, abstract No. 5169.

Stacher, Georg, Palonosetron Helsinn, Current Opinion in Investigational Drugs. Oct. 2002, vol. 3, No. 10, pp. 1502-1507.

Navari, Rudolph M., Pathogenesis-Based Treatment of Chemotherapy-Induced Nausea and Vomiting—Two New Agents, Journal of Supportive Oncology, 2003, vol. 1(2), pp. 89-103.

Chaitow, 1990, 3 pages.

Opposition Brief filed by Dr. Reddy's Laboratories (UK) Limited, opposition to European Patent No. 1601359 B1 dated Jul. 7, 2009.

Photolytic and oxidative degradation of an antiemetic agent, RG 12915 (Won C. M. et al., International Journal of Pharmaceutics 121, 95-105 (1995).

Palonosetron: a phase II dose ranging study to assess over a 7 day period the single dose pharmacokinetic profile of palonosetron in patients receiving highly emetogenic chemotherapy. Piraccini et al., Proc. Am. Soc. Clin. Oncol 2002 21 Abs 449 (2002).

Formulation and administration techniques to minimize injection pain and tissue damage associated with parenteral products. Larry A. Gatlin and Carol A. Brister Gatlin, from Injectable Drug Development: Techniques to Reduce Pain and Irritation (Edited by Pramod K. Gupta and Gayle A. Brazeau; published by Informa Health Care) 1999; ISBN 1574910957, 9781574910957, p. 401-421.

Parenteral Dosage Forms. Joanne Broadhead, from Part 11-Early drug development, pharmaceutical preformulation and formulation: a practice guide from candidate drug selection to commercial dosage form (Edited by Mark Gibson; Published by Interpharma Press, 2001; ISBN 1574911201, 9781574911206), p. 331-353.

Opposition Brief filed by Tecnimede Sociedade Tecnico-Medicinal S.A. in opposition to European Patent No. 1601359 B1, Jul. 8, 2009.

Response brief filed by Helsinn Healthcare S.A. dated Jul. 13, 2007, in response to the communication pursuant to Art. 96(2) EPC of Jan. 3, 2007 regarding Serial No. 04 706 657.6-2123.

European Patent Office official communication dated Jul. 19, 2006, regarding Serial No. 04 706 657.6.

Response of Helsinn Healthcare S.A. dated Nov. 29, 2006, regarding EPO official communication date Jul. 19, 2006.

Lachman et al., The Theory and Practice of Industrial Pharmacy, 1986, third edition, pp. 652-784.

Declaration of Valentino J. Stella, Ph.D. dated Sep. 19, 2007.

Opposition Brief filed by Martin Paul White, opposition to European Patent No. 1601359 B1, Jul. 8, 2009.

Wong et al. (1995), in British Journal of Pharmacology, vol. 114, pp. 851-859.

Cover page and pp. 642-644 and 783-784 of The Theory and Practice of Industrial Pharmacy, Third Edition, Lea and Febiger (1986).

Cover page and pp. 514-515 of Modern Pharmaceutics, Second Edition, Marcel Dekker (1990).

Cover page and pp. 142-143 of Pharmaceutical Dosage Forms: Parenteral Medications vol. 1, Second Edition, Marcel Dekker (1992).

Mitsuo Matsumoto et al., "Yakuzaigaku Manual", 1st edition, Nanzando Co., Ltd. (1989) 2 pages.

Michael J. Pikal, "Freeze Drying", Encyclopedia of Pharmaceutical Technology, Third Edition, Jan. 2007, pp. 1824-1825, vol. 3, Informa Pharmaceuticals and Healthcare.

Daniele Bonadeo, "Supplemental Declaration of Daniele Bonadeo Under 37 C.F.R. 1.132", filed in U.S. Appl. No. 11/388,270, Jun. 8, 2009.

Kranke et al., 2007 "Recent advances, trends, and economic considerations in . . . " Expert Opinion Pharmacotherp., 8(18): 3217-3235.

Morrow et al., 1995, "Progress in reducing nausea and emesis: Comparisons of ondansetron, granisetron, and tropisetron." Cancer, vol. 76, No. 3 pp. 343-357.

USPTO Notice of Allowance and Fees Due, U.S. Appl. No. 11/388,270, filed Mar. 24, 2006, Date Mailed Jan. 26, 2010.

USPTO Office Action, U.S. Appl. No. 11/129,839, Date Mailed Jan. 15, 2010.

Israili, Zafar H., "Clinical Pharmacology of Serotonin Receptor Type (5-HT3) Antagonists," Curr. Med. Chem. Central Nervous System Agents, 2001:1, 171-199.

Barton (Citrate Buffer Calculation) 2000, 2 pages.

USPTO Office Action, U.S. Appl. No. 11/201,035, Date Mailed Aug. 19, 2009.

Response of Helsinn Healthcare to opposition of EP Serial No. 04 706 657.6, dated Feb. 11, 2010.

Annex 1 (Statement of Walso Mossi, Ph.D.) to Response of Helsinn Healthcare to Opposition of EP Serial No. 04 706 657.6 dated Feb. 11, 2010.

Annex 2 to Response of Helsinn Healthcare to Opposition of EP Serial No. 04 706 657.6 dated Feb. 11, 2010.

Annex 3 to Response of Helsinn Healthcare to Opposition of EP Serial No. 04 706 657.6 dated Feb. 11, 2010.

Summary of Product Characteristics for Aloxi 250 (2009).

Scientific Discussion from the European Public Assessment Report for Aloxi (Palonoseteron Hydrochloride) 2006.

6th Edition, Handbook of Pharmaceutical Excipients (2009), pp. 247-250 (RPS Publishing).

Lewis, Gareth A (2006) 'Optimization Methods,' Encyclopedia of Pharmaceutical Technology, 1:1, 2452-2467.

May 24, 2011 Para. IV notice from Teva Pharmaceuticals re '724 and '725 patents.

May 24, 2011 Para. IV notice from Sandoz re '724 and '725 patents.

May 24, 2011 Para. IV notice from Dr. Reddy's re '724 and '725 patents.

Aug. 9, 2011 Para. IV notice from Dr. Reddy's re '424 patent.

Aug. 19, 2011 Para. IV notice from Teva Pharmaceuticals re '424 patent.

Sep. 22, 2011 Para. IV notice from Sandoz re '724, '725 and '424 patents.

Jul. 8, 2011 Complaint for patent infringement (D. N.J. case No. 11-03962).

Sep. 23, 2011 Complaint for patent infringement (D. N.J. case No. 11-5579).

Aug. 31, 2011 Answer and counterclaim of Dr. Reddy's Laboratories, Ltd. and Dr. Reddy's Laboratories, Inc. (D. N.J. case No. 11-03962).

Sep. 13, 2011 Sandoz Inc.'s answer to complaint for patent infringement and counterclaims (D. N.J. case No. 11-03962).

Sep. 13, 2011 Teva Pharmaceuticals USA, Inc. and Teva Pharmaceutical Industries Ltd.'s answer (D. N.J. case No. 11-03962).

Oct. 5, 2011 Plaintiff's reply to answer and counterclaim of Dr. Reddy's Laboratories, Ltd. and Dr. Reddy Laboratories, Inc. (D. N.J. case No. 11-03962).

Oct. 21, 2011 Plaintiffs reply to Sandoz Inc.'s answer to complaint for patent infringement and counterclaims (D. N.J. case No. 11-03962).

Oct. 24, 2011 Answer and counterclaim of Dr. Reddy's Laboratories, Ltd. and Dr. Reddy's Laboratories, Inc. (D. N.J. case No. 11-5579).

(56) **References Cited**

OTHER PUBLICATIONS

Oct. 24, 2011 Sandoz Inc.'s answer to complaint for patent infringement and counterclaims (D. N.J. case No. 11-5579).
Oct. 27, 2011 Order consolidating the two cases (D. N.J. case No. 11-5579).
Nov. 17, 2011 Plaintiffs' reply to answer and counterclaim of Dr. Reddy's Laboratories, Ltd. and Dr. Reddy's Laboratories, Inc. (D. N.J. case No. 11-03962).
Nov. 17, 2011 Plaintiffs' reply to Sandoz Inc.'s answer to complaint for patent infringement and counterclaims (D. N.J. case No. 11-03962).
Dec. 5, 2011 Teva Pharmaceuticals USA Inc. and Teva Pharmaceuticals Industries Ltd.'s answer to complaint for patent infringement of the '424 patent (D. N.J. case No. 11-03962).
May 21, 2012 Defendants' opening claim construction brief (including exhibits 1-31).
May 21, 2012 Plaintiffs' opening claim construction brief (including exhibits 1-15).
Jul. 20, 2012 Defendants' responsive claim construction brief (including exhibits 1-3).
Jul. 20, 2012 Plaintiffs' responsive claim construction brief (including Exhibits A and B).
Sep. 7, 2012 Court transcript from Sep. 7, 2012 Markman hearing and Plaintiffs' PowerPoint presentation (D. N.J. case No. 11-03962).
Dec. 1, 2011 Sandoz Inc.'s invalidity contentions pursuant to L. Pat. R. 3.6(c) (D. N.J. case No. 11-03962).
Dec. 1, 2011 Teva Pharmaceuticals USA, Inc. and Teva Pharmaceutical Industries, Ltd.'s invalidity contentions, pursuant to L. Pat. R. 3.6(c)(D. N.J. case No. 11-03962).
Dec. 1, 2011 Dr. Reddy's Laboratories, Ltd.'s and Dr. Reddy's Laboratories, Inc.'s invalidity contentions pursuant to L. Pat. R. 3.6(c) (D. N.J. case No. 11-03962).
Jan. 31, 2012 Plaintiffs responses to defendants' invalidity contentions (D. N.J. case No. 11-03962).
Sep. 25, 2012 Sandoz Inc.'s first amended invalidity contentions pursuant to L. Pat. R. 3.6(c) (D. N.J. case No. 11-03962).
Nov. 19, 2012 Plaintiffs' responses to Sandoz Inc.'s first amended invalidity contentions (D. N.J. case No. 11-03962).
L.G. Wade Jr., Organic Chemistry, Ch. 19: Amines, pp. 867-936 (Prentice Hall 3d ed. 1995).
L. Lachman et al., The Theory and Practice of Industrial Pharmacy, pp. 642-644, 783-784 (Lea & Febiger 3d ed. 1986).
P.P. DeLuca et al., Formulation of Small Volume Parenterals in Pharmaceutical Dosage Forms: Parenteral Medications, vol. 1, Ch. 5, pp. 173-248 (Avis, Lieberman, Lachman eds., Marcel Dekker Inc. 2d ed. 1992).
C.M. Won et al, Photolytic and Oxidative Degradation of an Antiemetic Agent, RGI2915, Int'l J Pharmaceutics 121:95-105 (1995).
R.D. Clark et al., 2-(Quinuciidin-3-yl)pyrido-[4,3-b]indol-I-ones and Isoquinoin-I-ones. Potent Conformationally Restricted 5-HT3 Receptor Antagonists, J Med. Chem. 36:2645-57 (1993).
L.A. Trissel, Drug Stability and Compatibility Issues, Handbook on Injectable Drugs, pp. XI-XVI (ASHP 7th ed. 1992).
J. Broadhead, Parenteral Dosage Forms, Pharmaceutical Preformulation and Formulation: A Practical Guide from Candidate Drug Selection to Commercial Dosage Form, Ch. 9, pp. 331-354 (Gibson ed., CRC Press 1st ed. 2001).
K.A. Connors et al., Chemical Stability of Pharmaceuticals: A Handbook for Pharmacists (John Wiley & Sons 2d ed. 1986).
Zofran®, in the Physician's Desk Reference, op. 1503-07 (5th ed. 2001).
Anzemet®, in The Physician's Desk Reference, pp. 680-683 (5th ed. 2001).
Kytril®, in The Physician's Desk Reference, pp. 3104-3106 (5th ed. 2001).
L.A. Trissel, Ondansetron HCI, in Handbook on Injectable Drugs, pp. 683-688 (ASHP 7th ed. 1992).
Navoban® (tropisetron HCI) Malaysian Prescribing Information (Sep. 2000).
Kytril® (granisetron HCI) South African Prescribing Information (Dec. 1993).
S. Motola and S. Agharkar, Preformulation Research of Parenteral Medications, Pharmaceutical Dosage Forms: Parenteral Medications, vol. 1, Ch. 4, pp. 115-172 (Avis, Lieberman, Lachman eds., Marcel Dekker Inc. 2d ed. 1992).
J. Wells, Pharmaceutical Preformuatlion: The Physicochemical Properties of Drug Substances, Ch. 5: Drug Stability, pp. 152-191 (Ellis Horwod Ltd. 1988).
J. Swarbrick and Boylan, Encyclopedia of Pharmaceutical Technology, Excipients Chapter: Their Role in Parenteral Dosage Forms, vol. 19(2):137-172 (Marcel Dekker, Inc. 2000).
Handbook of Pharmaceutical Excipients, 3d Ed., (Kibbe ed. Pharmaceutical Press 2000); pp. 140-143, 191-194, 324-238.
G. Stacher, Palonosetron (Helsinn), Curro. Opin. Investig. Drugs, 3(10) 1502-7 (2002).
Handbook of Modern Pharmaceutical Analysis, (S. Ahuja et al. ed., Academic Press, 2001).
Jun. 8, 2009 Bonadeo Declaration.
Jun. 8, 2009 Bonadeo Declaration, Exhibit 2.
Jun. 8, 2009 Bonadeo Declaration, Exhibit 3.
HELSN0117262-69 (2008).
HELSN0117270-312 (2012).
Feb. 13, 2007 Statutory Declaration of Daniele Bonadeo, with Exhibit A.
Nov. 21, 2007 Statutory Declaration of Giorgio Calderari, Daniele Bonadeo, Roberta Cannella, Enrico Braglia, and Riccardo Braglia.
Reddy's Paragraph IV notice regarding all three patents (D. N.J. Case No. 12-2867), dated Mar. 30, 2012.
May 11, 2012 Complaint for patent infringement filed by Helsinn and Roche (D. N.J. Case No. 12-2867).
Jun. 26, 2012 Notice of Reddy's motion to dismiss (D. N.J. Case. No. 12-2867).
Jun. 26, 2012 Dr. Reddy's Laboratories, Ltd.'s and Dr. Reddy's Laboratories, Inc.'s memorandum of law in support of their motion to dismiss or for summary judgment of non-infringement of U.S. patent No. 7,947,724 (D. N.J. Case No. 12-2867) (including Exhibits 1-10).
Aug. 16, 2012 Notice of Plaintiffs' cross-motion for partial summary judgment of infringement (D. N.J. Case No. 12-2867).
Aug. 6, 2012 Plaintiffs' opposition to Defendants' motion to dismiss or for summary judgment of noninfringement and cross-motion for partial summary judgment of infringement (D. N.J. Case No. 12-1867) (including exhibits 1-4).
Schöneich declaration (D. N.J. Case No. 12-2867) (Including Exhibits A and 1-24), dated Aug. 6, 2012.
Sep. 4, 2012 Reddy's brief in opposition to Plaintiffs' cross-motion for partial summary judgment and reply memorandum of law in further support of Reddy's motion to dismiss or for summary judgment of non-infringement (D. N.J. Case No. 12-2867)(Including Exhibits 1-4).
DeLuca Declaration (D. N.J. Case No. 12-2867)(Including exhibits A-J), dated Sep. 3, 2012.
Sep. 10, 2012 Plaintiffs' letter to Judge Cooper in response to Reddy's combined opposition to Plaintiffs' cross-motion for partial summary judgment and reply in support of Reddy's motion to dismiss or for summary judgment of noninfringement (D. N.J. Case No. 12-2867)(including exhibits A and B).
Sep. 14, 2012 Dr. Reddy's letter in response to Plaintiffs' Sep. 10, 2012 letter (D. N.J. Case No. 12-2867).
USPTO Office Action, U.S. Appl. No. 11/388,268, filed Mar. 24, 2006, Mail Date Mar. 29, 2010.
USPTO Non-Final Office Action, U.S. Appl. No. 11/186,311, mailed Aug. 30, 2006.
USPTO Non-Final Office Action, U.S. Appl. No. 11/186,311, mailed Oct. 5, 2007.
USPTO Non-Final Office Action, U.S. Appl. No. 11/186,311, mailed Oct. 6, 2008.
USPTO Final Office Action, U.S. Appl. No. 11/186,311, mailed May 20, 2009.
USPTO Advisory Action, U.S. Appl. No. 11/186,311, mailed Jul. 15, 2009.
USPTO Notice of Allowance and Fees Due, U.S. Appl. No. 11/186,311, mailed Mar. 4, 2011.

(56) **References Cited**

OTHER PUBLICATIONS

USPTO Notice of Allowability, U.S. Appl. No. 11/186,311, dated May 24, 2011.
USPTO Non-Final Office Action, U.S. Appl. No. 11/388,268, mailed Jul. 17, 2006.
USPTO Non-Final Office Action, U.S. Appl. No. 11/388,268, mailed Nov. 17, 2006.
USPTO Non-Final Office Action, U.S. Appl. No. 11/388,268, mailed Oct. 3, 2007.
USPTO Non-Final Office Action, U.S. Appl. No. 11/388,268, mailed Mar. 26, 2008.
USPTO Final Office Action, U.S. Appl. No. 11/388,268, mailed Nov. 12, 2008.
USPTO Non-Final Office Action, U.S. Appl. No. 11/388,268, mailed Jul. 15, 2009.
USPTO Notice of Allowance and Fees Due, U.S. Appl. No. 11/388,268, mailed Dec. 22, 2010.
USPTO Non-Final Office Action, U.S. Appl. No. 11/388,269, mailed Jul. 19, 2006.
USPTO Non-Final Office Action, U.S. Appl. No. 11/388,269, mailed Nov. 17, 2006.
USPTO Non-Final Office Action, U.S. Appl. No. 11/388,269, mailed Sep. 20, 2007.
USPTO Non-Final Office Action, U.S. Appl. No. 11/388,269, mailed Jul. 9, 2008.
USPTO Interview Summary, U.S. Appl. No. 11/388,269, dated Apr. 28, 2009.
USPTO Final Office Action, U.S. Appl. No. 11/388,269, mailed May 20, 2009.
USPTO Advisory Action, U.S. Appl. No. 11/388,269, mailed Jul. 15, 2009.
USPTO Notice of Abandonment, U.S. Appl. No. 11/388,269, mailed Dec. 18, 2009.
USPTO Non-Final Office Action, U.S. Appl. No. 11/388,270, mailed Jul. 13, 2006.
USPTO Interview Summary, U.S. Appl. No. 11/388,270, dated Aug. 3, 2006.
USPTO Non-Final Office Action, U.S. Appl. No. 11/388,270, mailed Nov. 16, 2006.
USPTO Non-Final Office Action, U.S. Appl. No. 11/388,270, mailed Sep. 20, 2007.
USPTO Interview Summary, U.S. Appl. No. 11/388,270, dated Dec. 14, 2007.
USPTO Non-Final Office Action, U.S. Appl. No. 11/388,270, mailed Mar. 25, 2008.
USPTO Final Office Action, U.S. Appl. No. 11/388,270, mailed Oct. 29, 2008.
USPTO Advisory Action, U.S. Appl. No. 11/388,270, mailed Jan. 23, 2009.
USPTO Non-Final Office Action, U.S. Appl. No. 11/388,270, mailed Jul. 9, 2009.
USPTO Interview Summary, U.S. Appl. No. 11/388,270, dated Nov. 12, 2010.
USPTO Notice of Allowance and Fees Due, U.S. Appl. No. 11/388,270, mailed Jan. 5, 2011.
USPTO Non-Final Office Action, U.S. Appl. No. 13/087,012, mailed Mar. 12, 2012.
USPTO Non-Final Office Action, U.S. Appl. No. 13/087,012, mailed Jul. 19, 2012.
USPTO Interview Summary, U.S. Appl. No. 13/087,012, dated Feb. 15, 2013.
USPTO Notice of Allowance and Fees Due, U.S. Appl. No. 13/087,012, mailed Feb. 27, 2013.
USPTO Response to Amendment under Rule 312, U.S. Appl. No. 13/087,012, mailed Apr. 4, 2013.
USPTO Non-Final Office Action, U.S. Appl. No. 11/129,839, mailed Jun. 10, 2008.
Eisenberg et al. 2004, "Efficacy, safety and pharmacokinetics of palonosetron in patients receiving highly emetogenic cisplatin-based chemotherapy: a dose-ranging clinical study." Annals of Oncology, vol. 15, pp. 330-337.
Mayron et al. 1996, "Stability and compatibility of granistron hydrochloride in i.v. solutions and oral liquids and during simulated Y-site injection with selected drugs." Am J Health-Sys Pharm, 53: 294-304.
Trissel et al. 1997, "Compatibility of granisetron hydrochloride with selected drugs during simulated Y -site administration." Am J Health-Syst Pharm 54: 56-60.
USPTO Final Office Action, U.S. Appl. No. 11/129,839, mailed Mar. 17, 2009.
USPTO Advisory Action, U.S. Appl. No. 11/129,839, mailed Jul. 22, 2009.
USPTO Non-Final Office Action, U.S. Appl. No. 11/129,839, mailed Jan. 15, 2010.
USPTO Examiner Interview Summary, U.S. Appl. No. 11/129,839, mailed Nov. 9, 2010.
USPTO Notice of Allowance and Fees Due, U.S. Appl. No. 11/129,839, mailed Jan. 3, 2011.
USPTO Notice of Abandonment, U.S. Appl. No. 11/129,839, mailed Apr. 18, 2011.
USPTO Non-Final Office Action, U.S. Appl. No. 13/077,374, mailed Feb. 17, 2012.
Roila et al. 1998, "Prevention of chemotherapy- and radiotherapy-induced emesis: Results of the Perugia consensus conference." Annals of Oncology, vol. 9, pp. 811-819.
USPTO Final Office Action, U.S. Appl. No. 13/077,374, mailed Nov. 23, 2012.
Piraccini, Gaia et al., American Society of Clinical Oncology May 12-15, 2001 San Francisco-USA (vol. 20, part 1 of 2, 2001) (Abstract No. 1595).
USPTO Non-Final Office Action, U.S. Appl. No. 11/201,035, mailed May 16, 2008.
USPTO Final Office Action, U.S. Appl. No. 11/201,035, mailed Feb. 4, 2009.
USPTO Final Office Action, U.S. Appl. No. 11/201,035, mailed Jun. 8, 2010.
FDA approval letter of Aloxi (palonosetron hydrochloride injection), dated Jul. 25, 2003.
Macciocchi A, Chernoff SB, Gallagher SC. A phase II dose-ranging study to assess intravenous doses of palonosetron for the prevention of highly emetogenic chemotherapy-induced nausea and vomiting. In: Program/Proceedings of the 38th Annual Meeting of the American Society of Clinical Oncology; May 18-21, 2002; Orlando, Fla. Abstract 1480.
Grunberg SM, Hajdenberg J, Charu V, et al. Palonosetron is active in preventing acute and delayed emesis following moderately emetogenic chemotherapy: results of a phase III trial. Support Care Cancer 2002; 10:Abstract P-113.
Aapro MS, Selak E, Lichinitser M, et al. Palonosetron is more effective than ondansetron in preventing chemotherapy-induced nausea and vomiting in patients receiving moderately emetogenic chemotherapy: results of a phase III trial. In: Program/Proceedings of the 39th Annual Meeting of the American Society of Clinical Oncology; May 31-Jun. 3, 2003; Chicago, III. Abstract 2918.
Aapro MS, Bertoli L, Lordick F, et al. Palonosetron is effective in preventing acute and delayed chemotherapy induced nausea and vomiting in patients receiving highly emetogenic chemotherapy. 15th MASCC International Symposium, Berlin, Germany. Support Care Cancer, vol. 11, No. 6, Jun. 2003, A17.
Cartmell AD, Ferguson S, Yanagihara R, et al. Protection against chemotherapy-induced nausea and vomiting is maintained over multiple cycles of moderately or highly emetogenic chemotherapy by palonosetron, a potent 5 HT3 receptor antagonist. In: Program/Proceedings of the 39th Annual Meeting of the American Society of Clinical Oncology; May 31-Jun. 3, 2003; Chicago, III. Abstract 3041.
Sabra, Choice of a 5-HT3 Receptor Antagonist for the Hospital Formulary, EHP, Oct. 1996, vol. 2, Supp 1, S19-S24.
Gregory and Ettinger, 5HT3 receptor antagonists for the prevention of chemotherapy-induced nausea and vomiting. A comparison of their pharmacology and clinical efficacy. Drugs, Feb. 1998; 55(2): 173-189.

(56) **References Cited**

OTHER PUBLICATIONS

Full Prescribing Information for Aloxi (palonosetron HCI) injection for Intravenous Use (2008).
Drug, Dose & Schedule Recommendations for Antiemetic Regimens (American Society for Clinical Oncology) (2006).
Yamakuni, et al., The Journal of Pharmacology and Experimental Therapeutics, Probable Involvement of the 5-Hydroxytryptamine4 Receptor in Methotrexate-Induced Delayed Emesis in Dogs, 2000, The American Society for Pharmacology and Experimental Therapeutics, vol. 292, No. 3, p. 1002-1294.
Geling, et al., Should 5-Hydroxytryptamine-3 Receptor Antagonists Be Administered Beyond 24 Hours After Chemotherapy to Prevent Delayed Emesis? Systematic Re-Evaluation of Clinical Evidence and Drug Cost Implications, Journal of Clinical Oncology, vol. 23, No. 6, Feb. 20, 2005 (American Society of Clinical Oncology), pp. 1289-1294.
Rojas, et al., International Anesthesia Research Society, Palonosetron Exhibits Unique Molecular Interactions with 5-HT3 Receptor, vol. 107, No. 2, Aug. 2008, p. 469-478.
Rojas, et al., Palonosetron triggers 5-HT3 receptor internalization and causes inhibition of receptor function, European Journal of Pharmacology 626 (2010), p. 193-199.
Regan-Shaw, et al., Dose translation from animal to human studies revisited, The FASEB Journal, Life Sciences Forum, p. 659-661.
Saito, et al., Palonosetron plus dexamethasone versus granisetron plus dexamethasone for prevention of anusea and vomiting during chemotherapy: a double-blind, double-dummy, randomised, comparative phased III trial, www.thelancet.com/oncology, vol. 10, Feb. 2009, p. 115-124.
Palonosetron: more than just another option?. www.thelancet.com/oncology, vol. 10, Feb. 2009, p. 100-101.
Lorusso, et al., Single dose of palonosetron plus dexamethasone to control nausea, vomiting and to warrant an adequate food intake in patients treated with highly emetogenic chemotherapy (HEC). Preliminary results, Support Care Cancer, published online Mar. 18, 2009.
Grunberg, et al., Effectiveness of a single-day three-drug regimen of dexamethasone, palonosetron, and aprepitant for the prevention of acute and delayed nausea and vomiting caused by moderately emetogenic chemotherapy, Support Care Cancer (2009) 17:589-594.
Celio, et al., Clinical update on palonosetron in the management of chemotherapy-induced nausea and vomiting, Tumor, 94: 447-452, 2008.
Ellebaek, et al., Optimizing antiemetic therapy in multiple-day and multiple cycles of chemotherapy, Lippincott williams & Wilkins, Current Opinion in Supportive and Palliative Care, 2008, 2:28-34.
Herrington, et al., Randomized, Placebo-controlled, Pilot Study Evaluating Aprepitant Single Dose Plus Palonosetron and Dexamethasone for the Prevention of Acute and Delayed Chemotherapy-induced Nausea and Vomiting, American Cancer Society, published online Mar. 7, 2008 in Wiley InterScience (www.interscience.wiley.com).
Massa, et al., Palonosetron plus dexamethasone effectively prevents acute and delayed chemotherapy-induced nausea and vomiting following highly or moderately emetogenic chemotherapy in pretreated patients who have failed to respond to a previous antiemetic treatment: Comparison between elderly and non-elderly patient response, Critical Reviews in Oncology/Hematology 70 (2009) 83-91.
2006 Update of the ASCO Recommendations for Antiemetics in Oncology: Guideline Summary, American Cancer Society of Clinical Oncology, Jul. 2006, www.jopasco.org.
Warr, David, Standard treatment of chemotherapy-induced emesis, Support Care Cancer, vol. 5, pp. 12-16, 1997.
Aapro, M.S., et al. A phase III, double-blind, randomized trial of palonosetron compared with ondansetron in preventing chemotherapy-induced nausea and vomiting following highly emetogenic chemotherapy. Annals of Oncology, vol. 17, pp. 1441-1449, 2006.
Eisenberg, Peter, et al. Improved Prevention of Moderately Emetogenic Chemotherapy-Induced Nausea and Vomiting with Palonosetron, a Pharmacologically Novel5-HT3 Receptor Antagonist. Cancer, vol. 98, No. 11, pp. 2473-2482, Dec. 1, 2003.
Gandara, D.R., et al. The delayed-emesis syndrome from cisplatin: Phase III evaluation of ondansetron versus placebo. Semin Oneal vol. 19, No. 4, pp. 67-71, Aug. 1992 (suppl 10).
Goedhals, L., et al. Control of delayed nausea and vomiting with granisetron plus dexamethasone or dexamethasone alone in patients receiving highly emetogenic chemotherapy: A double-blind, placebo-controlled, comparative study. Ann Oneal, vol. 9, pp. 661-666, 1998.
Gralla, R., et al. Palonosetron improves prevention of chemotherapy-induced nausea and vomiting following moderately emetogenic chemotherapy: results of a double-blind randomized phase III trial comparing single doses of palonosetron with ondansetron. Annals of Oncology, vol. 14, pp. 1570-1577, 2003.
Italian Group for Antiemetic Research. Dexamethasone alone or in combination with ondansetron for the prevention of delayed nausea and vomiting induced by chemotherapy. N Engl J Med, vol. 342, No. 21, pp. 1554-1559, May 25, 2000.
Kaizer, L., et al. Effect of schedule and maintenance on the antiemetic efficacy of ondansetron combined with dexamethasone in acute and delayed nausea and emesis in patients receiving moderately emetogenic chemotherapy: A phase III trial by the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol, vol. 12, No. 5, pp. 1050-1057, May 1994.
Latreille, J., et al. Use of dexamethasone and granisetron in the control of delayed emesis for patients who receive highly emetogenic chemotherapy: National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol, vol. 16, No. 3, pp. 1174-1178, Mar. 1998.
Antiemetic Subcommittee of the Multinational Association of Supportive Care in Cancer (MCSCC). Prevention of chemotherapy- and radiotherapy-induced emesis: Results of the Perugia Consensus Conference. Annals of Oncology, vol. 9, pp. 811-819, 1998.
Moyer, Paula. New Understanding of Emesis Pathways Leading to New Treatment, Better Control. Oncology Times, vol. 25, Issue 10, pp. 48-51, May 25, 2003.
Navari, R.M., et al. Oral ondansetron for the control of cisplatin-induced delayed emesis: A large, multicenter, double-blind, randomized comparative trial of ondansetron versus placebo. J Clin Oncol, vol. 13, No. 9, pp. 2408-2416, Sep. 1995.
Olver, I., et al. A multicenter, double-blind study comparing placebo, ondansetron and ondansetron plus dexamethasone for the control of cisplatin-induced delayed emesis. Ann Oncol, vol. 7, pp. 945-952, 1996.
Pater, J.L., et al. The role of the 5-HT3 antagonists ondansetron and dolasetron in the control of delayed onset nausea and vomiting in patients receiving moderately emetogenic chemotherapy. Ann Oncol, vol. 8, pp. 181-185, 1997.
Rojas, Camilo, et al. The Antiemetic 5-HT3 Receptor Antagonist Palonosetron Inhibits Substance P-Mediated Responses In Vitro and In Vivo. J Pharmacal Exper Thera, vol. 335, No. 2, pp. 362-368, 2010.
Sorbe, B. G., et al. A study evaluating the efficacy and tolerability of tropisetron in combination with dexamethasone in the prevention of delayed platinum-induced nausea and emesis. Cancer, vol. 83, pp. 1022-1032, 1998.
Stewart, A., et al. Ondansetron Compared with Granisetron in the Prophylaxis of Cyclophosphamide-Induced Emesis in Out-Patients: A Multicentre, Double-Blind, Double-Dummy, Randomised, Parallel-Group Study. Oncology, vol. 52, pp. 202-210, 1995.
Weiderpass, Elisabete, et al. Use of an NK1 Receptor Antagonist to Prevent Delayed Emesis After Cisplatin. Journal of the National Cancer Institute, vol. 89, No. 11, pp. 817-818, Jun. 4, 1997.
Akers, Michael J., Excipient-Drug Interactions in Parenteral Formulations. Journal of Pharmaceutical Sciences, vol. 91, No. 11, Nov. 2002, pp. 2283-2300.
Maemondo, et al., A phase II study of palonosetron combined with dexamethasone to prevent nausea and vomiting induced by highly emetogenic chemotherapy. Annals of Oncology, Nov. 2009, vol. 20, No. II, pp. 1860-1866.
Program/Proceedings American Society of Clinical Oncology, vol. 20, Part 1 of 2, 2001, Abstract No. 1595 and associated poster presentation.

(56) **References Cited**

OTHER PUBLICATIONS

Saito, et al., Review of palonosetron: emerging data distinguishing it as a novel 5-HT3 receptor antagonist for chemotherapy-induced nausea and vomiting. Expert Opin. Pharmacother (2010) II (6), pp. 1003-1014.
MGI-HHC_SEC_filing (2001).
ROCHE0008749-876 (1995) (portions redacted).
HELSN0135068-82 (1998) (portions redacted).
English-language translation of Italian-language portions of HELSN0135068-82 (1998).
HELSN0161327-348 (2000) (portions redacted).
HELSN0138407-24 (1998) (portions redacted).
HELSN0376401-469 (2002) (portions redacted).
HELSN0392650-72 (1999) (portions redacted).
Dr. Reddy's Labs., Ltd.'s and Dr. Reddy's Labs., Inc.'s Memorandum of Law in Support of Their Motion to Amend Their Invalidity Contentions dated Feb. 15, 2013 (D.N.J. Case No. 11-3962).
HELSN0376719-21 (2001) (cited in 700).
HELSN0376722-23 (2001) (cited in 700).
HELSN0376724 (2002) (cited in 700).
Dr. Reddy's Laboratories, Ltd.'s and Dr. Reddy's Laboratories, Inc.'s Redline of Proposed Amended Invalidity Contentions Pursuant to L. Pat. R. 3.6(c) filed Feb. 15, 2013 (D.N.J. Case No. 11-3962).
Dr. Reddy's Laboratories, Ltd.'s and Dr. Reddy's Laboratories, Inc.'s Reply Memorandum of Law in Further Support of Their Motion to Amend Their Invalidity Contentions dated Mar. 15, 2013 (D.N.J. Case No. 11-3962).
Teva Pharm. Indus., Ltd.'s and Teva Pharm. USA, Inc.'s Memorandum in Support of Their Motion to Amend Invalidity Contentions dated Feb. 15, 2013 (D.N.J. Case No. 1-3962).
HELSN0388553-65 (1998) (cited in 706; portions redacted).
HELSN0388566-68 (1998) (cited in 706; portions redacted).
HELSN0388569-74 (1998) (cited in 706; portions redacted).
HELSN0388587-91 (1998) (cited in 706; portions redacted).
HELSN0388592-95 (1998) (cited in 706; portions redacted).
English-language translation of HELSN0388592-95 (1998) (cited in 706; portions redacted).
HELSN0388596-97 (1998) (cited in 706; portions redacted).
HELSN0388604 (1998) (cited in 706; portions redacted).
HELSN0388605-06 (1998) (cited in 706; portions redacted).
HELSN0388607-09 (1998) (cited in 706; portions redacted).
HELSN0389134-44 (1999) (cited in 706; portions redacted).
HELSN0389145-48 (1999) (cited in 706; portions redacted).
HELSN0389149-61 (2000) (cited in 706; portions redacted).
HELSN0392047-48 (1998) (cited in 706; portions redacted).
HELSN0392393-94 (1998) (cited in 706; portions redacted).
HELS0393657-61 (2000) (cited in 706; portions redacted).
English-language translation of Italian-language portions of HELSN039657-61 (2000) (cited in 706; portions redacted).
Excerpts from Calderari Deposition Transcript, pp. 1-4, 229-232, and 278-393 (2013) (cited in 706 and 728; portions redacted).
HELSN0000093-9 (2006) (cited in 724; portions redacted).
HELSN0004207 (2002) (cited in 724).
HELSN0004217 (2002) (cited in 724).
Teva Pharm. Indus., Ltd.'s and Teva Pharm. USA, Inc.'s Reply in Support of Their Motion to Amend Their Invalidity Contentions dated Mar. 15, 2013 (D.N.J. Case No. 1-3962).
HELSN00388448-542 (1998-1999) (cited in 728; portions redacted).
English-language translation of Italian-language portions of HELSN00388448-542 (1998-1999) (portions redacted).
HELSN0388543-44 (1999) (cited in 728; portions redacted).
HELSN0388545-52 (1998) (cited in 728; portions redacted).
HELSN0388575-76 (1998) (cited in 728; portions redacted).
HELSN0388577-80 (1998) (cited in 728; portions redacted).
HELSN0388581-82 (1998) (cited in 728; portions redacted).
HELSN0388583-84 (1998) (cited in 728; portions redacted).
HELSN0388585 (1998) (cited in 728; portions redacted).
HELSN0388586 (1998) (cited in 728; portions redacted).
HELSN0388598-601 (1998) (cited in 728; portions redacted).
HELSN0388602-03 (1998) (cited in 728; portions redacted).
HELSN0388610 (1998) (cited in 728; portions redacted).
Sandoz Inc.'s Redacted Memorandum of Law in Support of its Motion to Amend its Invalidity Contentions dated Feb. 15, 2013 (D.N.J. Case No. 11-3962).
Exhibit G to Sandoz Inc.'s Redacted Memorandum of Law in Support of its Motion to Amend its Invalidity Contentions dated Feb. 15, 2013 (D.N.J. Case No. 11-3962) (cited in 742).
Sandoz Inc.'s Redacted Reply Memorandum of Law in Support of its Motion to Amend its Invalidity Contentions dated Mar. 15, 2013 (D.N.J. Case No. 11-3962).
Aurobindo Pharma Ltd. Paragraph IV notice regarding U.S. Patent Nos. 7,947,724; 7,947,725; and 7,960,424, dated Mar. 5, 2013 (D. Del. Case No. 13-688).
Complaint for patent infringement filed by Helsinn Healthcare S.A. and Roche Palo Alto LLC against Aurobindo Pharma Ltd. And Aurobindo Pharma USA Inc. dated Apr. 16, 2013 (D. Del. Case No. 13-688).
Accord Healthcare, Inc. Paragraph IV notice regarding U.S. Patent Nos. 7,947,724; 7,947,725; and 7,960,424, dated Apr. 3, 2013.
Drug Marketing Approval Document for Aloxi I.V. Drip Infusion Bag 0.75 mg, Japanese Ministry of Health, Labour and Welfare (2012).
English-language translation of Cite No. 800 (2012).
Approval of Partial Changes in Drug Marketing Approved Items for Aloxi I.V. Drip Infusion Bag 0.75 mg, Japanese Ministry of Health, Labour and Welfare (2012).
English-language translation of Cite No. 802 (2012).
Feb. 9, 2009 Bonadeo Declaration.
Bedford Laboratories division of Ben Venue Laboratories, Inc. Paragraph IV Letter regarding U.S. Patent Nos. 7,947,724, 7,947,725, and 7,960,424, dated Aug. 13, 2013.
Aurobindo Pharma Ltd. Paragraph IV notice regarding U.S. Patent No. 8,518,981, dated Sep. 19, 2013.
Dr. Reddy's Laboratories, Ltd.'s and Dr. Reddy's Laboratories, Inc.'s Amended Invalidity Contentions Pursuant to L. Pat. R. 3.6(c), dated Jul. 8, 2013 (D.N.J. Case Nos. 11-3962 and 11-5579; consolidated).
Sandoz Inc.'s Second Amended Invalidity Contentions Pursuant to L. Pat. R. 3.7, dated Jul. 5, 2013 (D.N.J. Case Nos. 11-3962 and 11-5579; consolidated) (confidentiality designation and other portions redacted).
Defendants Teva Pharmaceuticals USA, Inc. and Teva Pharmaceutical Industries, Ltd.'s First Amended Invalidity Contentions Pursuant to L. Pat. R. 3.6(c), dated Jul. 5, 2013 (D.N.J. Case Nos. 11-3962 and 11-5579; consolidated) (confidentiality designation redacted).
Opening Expert Report of Dr. Bert Spilker, dated Sep. 9, 2013 (D.N.J. Case Nos. 11-3962 and 11-5579; consolidated) (confidentiality designation and other portions redacted).
Expert Report of David G. Frame, Pharm.D., dated Sep. 5, 2013 (D.N.J. Case Nos. 11-3962 and 11-5579; consolidated) (confidentiality designation and other portions redacted).
Expert Report of Lee Kirsch, Ph.D., dated Sep. 9, 2013 (D.N.J. Case Nos. 11-3962 and 11-5579; consolidated) (confidentiality designation and other portions redacted).
Expert Report of Patrick P. DeLuca, Ph.D., dated Sep. 9, 2013 (D.N.J. Case Nos. 11-3962 and 11-5579; consolidated) (confidentiality designation and other portions redacted).
Expert Report of Paul Myrdal, Ph.D., dated Sep. 9, 2013 (D.N.J. Case Nos. 11-3962 and 11-5579; consolidated) (confidentiality designation and other portions redacted).
Complaint for patent infringement filed by Helsinn Healthcare S.A. and Roche Palo Alto LLC against Ben Venue Laboratories, Inc. d/b/a Bedford Laboratories regarding U.S. Patent Nos. 7,947,724, 7,947,725, 7,960,424, and 8,518,981 dated Sep. 25, 2013 (D. Del. Case No. 13-1612).
Reply Expert Report of Patrick P. DeLuca, Ph.D., dated Nov. 22, 2013 (D.N.J. Case Nos. 11-3962 and 11-5579; consolidated) (confidentiality designation redacted).
Reply Expert Report of David G. Frame, Pharm. D., dated Nov. 27, 2013 (D.N.J. Case Nos. 11-3962 and 11-5579; consolidated) (confidentiality designation redacted).

(56) **References Cited**

OTHER PUBLICATIONS

Reply Expert Report of Jack Geltosky, Ph.D., dated Nov. 22, 2013 (D.N.J. Case Nos. 11-3962 and 11-5579; consolidated) (confidentiality designation and other portions redacted).
Reply Expert Report of Lee Kirsch, Ph.D., dated Nov. 22, 2013 (D.N.J. Case No. 11-3962 and 11-5579; consolidated) (confidentiality designation redacted).
Reply Expert Report of Paul Myrdal, Ph.D., dated Nov. 22, 2013 (D.N.J. Case No. 11-3962 and 11-5579; consolidated) (confidentiality designation redacted).
Reply Expert Report of Dr. Bert Spilker, dated Nov. 22, 2013 (D.N.J. Case No. 11-3962 and 11-5579; consolidated) (confidentiality designation and other portions redacted).
Accord Healthcare, Inc. Paragraph IV Letter regarding U.S. Patent No. 8,518,981 dated Oct. 2, 2013 (portions redacted).
Bedford Laboratories division of Ben Venue Laboratories, Inc. Paragraph IV Letter regarding U.S. Patent No. 8,518,981 dated Oct. 16, 2013 (portions redacted).
Sandoz Inc. Paragraph IV Letter regarding U.S. Patent No. 8,518,981 dated Dec. 16, 2013.
Aurobindo Pharma Ltd. Paragraph IV Letter regarding U.S. Patent Nos. 8,598,218 and 8,598,219 dated Jan. 21, 2014 (portions redacted).
Sandoz Inc. Paragraph IV Letter regarding U.S. Patent Nos. 8,598,218 and 8,598,219 dated Feb. 3, 2014 (portions redacted).
Bedford Laboratories division of Ben Venue Laboratories, Inc. Paragraph IV Letter regarding U.S. Patent Nos. 8,598,218 and 8,598,219 dated Feb. 6, 2014 (portions redacted).
Defendants Aurobindo Pharma Ltd.'s and Auromedics Pharma LLC's Amended Answer, Affirmative Defenses, and Counterclaims regarding U.S. Patent Nos. 7,947,724, 7,947,725, 7,960,424, 8,518,981, 8,598,218, and 8,598,219, dated Feb. 11, 2014 (D. Del. Case No. 13-688).
Ben Venue Laboratories, Inc.'s Answer and Counterclaims to Amended Complaint regarding U.S. Patent Nos. 7,947,724, 7,947,725, 7,960,424, 8,518,981, 8,598,218, and 8,598,219, dated Feb. 24, 2014 (D. Del. Case No. 13-1612).
Complaint for Patent Infringement filed by Helsinn Healthcare S.A. and Roche Palo Alto LLC against Accord Healthcare, Inc. and Intas Pharmaceuticals Ltd regarding U.S. Patent Nos. 8,598,218 and 8,598,219 dated Dec. 27, 2013 (D. Del. Case No. 13-2101).
Cipla Limited Paragraph IV Letter regarding U.S. Patent Nos. 7,947,724, 7,947,725, 7,960,424, 8,518,981, 8,598,218, and 8,598,219 dated Feb. 24, 2014 (portions redacted).
Dr. Reddy's Laboratories, Ltd.'s and Dr. Reddy's Laboratories, Inc.'s Invalidity Contentions regarding U.S. Patent Nos. 8,518,981, 8,598,218, and 8,598,219 dated Mar. 17, 2014 (D.N.J. Case No. 13-5815) (confidentiality designation and other portions redacted).
Sandoz Inc.'s Invalidity Contentions Pursuant to L. Pat. R. 3.3 and 3.6(c) regarding U.S. Patent Nos. 8,518,981, 8,598,218, and 8,598,219 dated Mar. 17, 2014 (D.N.J. Case No. 13-5815) (confidentiality designation and other portions redacted).
Teva Pharmaceuticals USA, Inc. and Teva Pharmaceutical Industries Ltd.'s Invalidity Contentions Pursuant to L. Pat. R. 3.6(c) regarding U.S. Patent Nos. 8,518,981, 8,598,218, and 8,598,219 dated Mar. 17, 2014 (D.N.J. Case No. 13-5815) (confidentiality designation and other portions redacted).
USPTO Non-Final Office Action, U.S. Appl. No. 14/070,981, mailed Nov. 4, 2014.
Mylan Institutional LLC's Opening Claim Construction Brief dated Dec. 5, 2014 (D. Del. Case No. 13-688, consolidated).
Defendants Cipla Ltd. And Cipla USA, Inc.'s Corrected Opening Claim Construction Brief dated Jan. 27, 2015 (D. Del. Case No. 13-688, consolidated).
Plaintiffs' Opening Claim Construction Brief dated Dec. 5, 2014 (D. Del. Case No. 13-688, consolidated).
Defendants Teva Pharmaceuticals USA, Inc. and Teva Pharmaceutical Industries Ltd. Corrected Answer to Complaint for Patent Infringement and Counterclaim for Declaratory Judgment regarding U.S. Patent No. 8,729,094 dated Jan. 8, 2015 (D.N.J. Case No. 14-6341).
Termination of the Proceeding (Case No. PGR2014-00010) dated Nov. 24, 2014.
Gavis Pharma LLC's Paragraph IV Letter regarding U.S. Patent Nos. 7,947,724, 7,947,725, 7,960,424, 8,518,981, 8,598,218, 8,598,219, and 8,729,094, dated Dec. 31, 2014 (portions redacted).
Answer, Defenses, and Counterclaims of Defendants Exela Pharma Sciences, LLC, Exela Pharmsci, Inc. and Exela Holdings, Inc. to Complaint regarding U.S. Patent Nos. 8,518,981 and 8,598,218 redacted version dated Dec. 29, 2014 (D. Del. Case No. 14-1444).
Defendant Mylan Institutional, LLC's Responsive Claim Construction Brief dated Jan. 14, 2015 (D. Del. Case No. 13-688, consolidated).
Defendants Cipla Ltd. and Cipla USA, Inc.'s Corrected Answering Claim Construction Brief dated Jan. 27, 2015 (D. Del. Case No. 13-688, consolidated).
Plaintiffs' Responsive Claim Construction Brief, redacted public version dated Jan. 20, 2015 (D. Del. Case No. 13-688, consolidated).

* cited by examiner

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_3 (5-hydroxytryptamine) receptor antagonists has been developed that treat such emesis by antagonizing cerebral functions associated with the 5-HT_3 receptor. See *Drugs Acting on 5-Hydroxytryptamine Receptors*: The Lancet Sep. 23, 1989 and references cited therein. Drugs within this class include ondansetron, granisetron, alosetron, tropisetron, and dolasetron. These 5-HT_3 antagonists are often administered intravenously shortly before chemotherapy or radiotherapy is initiated, and can be administered more than once during a cycle of chemotherapy or radiotherapy. In addition, they are often supplied as tablets or oral elixirs to either supplement an intravenous administration, or to ease home usage of the drug if the patient is self-administering the chemotherapeutic regimen.

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

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

Ingredient	Mg
Palonosetron 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 (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® (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_3 receptor antagonist and its pharmaceutically acceptable carriers that would facilitate making a formulation with this increased stability.

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

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

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

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

SUMMARY OF THE INVENTION

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

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

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

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

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

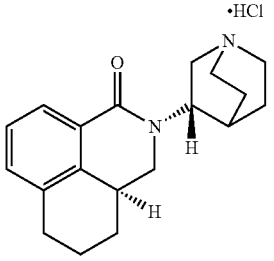
DETAILED DESCRIPTION OF THE INVENTION

Definitions

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

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

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



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

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

"Pharmaceutically acceptable salts" means salts which are pharmaceutically acceptable, as defined above, and which possess the desired pharmacological activity. Such salts include acid addition salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or with organic acids such as acetic acid, propionic acid, hexanoic acid, heptanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, o-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2,-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid p-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, p-toluenesulfonic acid, camphorsulfonicacid, 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

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

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

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

- The formulation may comprise palonosetron or a pharmaceutically acceptable salt thereof in a concentration from about 0.02 mg/mL to about 1.0 mg/mL, from about 0.03 mg/mL to about 0.2 mg/mL palonosetron hydrochloride, and most optimally about 0.05 mg/ml.
- The formulation may comprise citrate buffer in a concentration of from about 10 to about 40 millimoles, or 15-30 millimoles.
- The formulation may comprise EDTA in a concentration of from about 0.005 mg/ml to about 1.0 mg/ml, or about 0.3 to about 0.7 mg/ml, and most optimally about 0.5 mg/ml.

The inventors have further discovered that the addition of mannitol and a chelating agent can increase the stability of palonosetron formulations. Therefore, in still another embodiment the invention provides a pharmaceutically stable solution for preventing or reducing emesis comprising a) palonosetron or a pharmaceutically acceptable salt thereof and b) a pharmaceutically acceptable carrier, wherein the pharmaceutically acceptable carrier comprises a chelating agent and mannitol. Similarly, in another embodiment the invention provides a method of formulating a pharmaceutically stable solution of palonosetron comprising admixing a) palonosetron or a pharmaceutically acceptable salt thereof and b) a pharmaceutically acceptable carrier, wherein the pharmaceutically acceptable carrier comprises a chelating agent and mannitol. The chelating agent is preferably EDTA, and, in various embodiments the chelating agent is present in a concentration of from about 0.005 to about 1.0 mg/mL or from about 0.05 mg/mL to about 1.0 mg/mL or from about 0.3 to about 0.7 mg/ml, or most optimally about 0.5 mg/mL. In various embodiments the mannitol is present in a concentration of from about 10.0 mg/ml to about 80.0 mg/ml, from about 20.0 mg/mL to about 60.0 mg/ml, or from about 40.0 to about 45.0 mg/ml.

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

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

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

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

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

EXAMPLES

Example 1

Stabilizing pH

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

Example 2

Stabilizing Concentration Ranges

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

Example 3

Tonicifying Agent

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

Example 4

Formulation I

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

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

*calculated as a free base

Example 5

Formulation II

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

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

*calculated as a free base

Example 6

Stability of Palonosetron without Dexamethasone

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

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

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

Example 7

Stability of Palonosetron with Dexamethasone

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

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

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

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

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[a)]
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[b)] plus rubber stopper[c)]

[a)]Calculated based on the weight of free base
[b)]Polyethylene multilayer film infusion bag.
[c)]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

US009173942B2

(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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(*) 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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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.

(51) **Int. Cl.**

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A61K 47/18	(2006.01)
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A61K 47/00	(2006.01)
A61K 31/473	(2006.01)
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(58) **Field of Classification Search**

USPC 514/397

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,695,578	A	9/1987	Coates et al.
4,753,789	A	6/1988	Tyers et al.
4,886,808	A	12/1989	King
4,906,755	A	3/1990	Gittos
4,929,632	A	5/1990	Tyers et al.
4,937,247	A	6/1990	King
5,011,846	A	4/1991	Gittos et al.
5,034,398	A	7/1991	King
5,202,333	A	4/1993	Berger et al.
5,240,954	A	8/1993	Tyers et al.
5,272,137	A	12/1993	Blase et al.
5,344,658	A	9/1994	Collin
5,578,628	A	11/1996	Tyers et al.
5,578,632	A	11/1996	Tyers et al.
5,622,720	A	4/1997	Collin
5,854,270	A	12/1998	Gambhir
5,922,749	A	7/1999	Tyers et al.
5,955,488	A	9/1999	Winterborn
6,063,802	A	5/2000	Winterborn
6,132,758	A	10/2000	Munayyer et al.
6,284,749	B1	9/2001	Castillo et al.
6,287,592	B1	9/2001	Dickinson
6,294,548	B1	9/2001	James
6,699,852	B2	3/2004	Robichaud
7,109,339	B2	9/2006	Lee et al.
7,947,724	B2	5/2011	Calderari et al.
7,947,725	B2	5/2011	Calderari et al.

(Continued)

FOREIGN PATENT DOCUMENTS

EP	0 512 400 A1	4/1992
WO	WO-03100091	12/2003

(Continued)

OTHER PUBLICATIONS

Tang et al., (Anesth Analg 1998; 87 462-467; Ref. 105.*

R. M. Eglen et al., "Pharmacological characterization of RS 25259-197, a novel and selective 5-HT3 receptor antagonist, in vivo," Br. J Pharmacology 114:860-866 (1995).

Chelly, Jacques et al., Oral RS-25259 Prevents Postoperative Nausea and Vomiting Following Laparoscopic Surgery, Anesthesiology, 1996, vol. 85, No. 3A, p. A21.

Sorbe, Bengt, 5-HT-3 Receptor Antagonists as Antiemetic Agents in Cancer Chemotherapy, extracted from Expert Opinion on Investigational Drugs, 1996, vol. 5 No. 4, pp. 389-407.

(Continued)

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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

(56) **References Cited**

U.S. PATENT DOCUMENTS

7,960,424	B2	6/2011	Calderari et al.
8,518,981	B2	8/2013	Calderari et al.
8,598,218	B2	12/2013	Calderari et al.
8,598,219	B2	12/2013	Calderari et al.
8,729,094	B2	5/2014	Calderari et al.
9,066,980	B2	6/2015	Calderari et al.
2001/0020029	A1	9/2001	James
2003/0095926	A1	5/2003	Dugger, III
2004/0147510	A1	7/2004	Landau et al.
2013/0261149	A1	10/2013	Calderari et al.
2013/0261150	A1	10/2013	Calderari et al.
2013/0289065	A1	10/2013	Calderari et al.
2014/0039000	A1	2/2014	Calderari et al.
2015/0141454	A1	5/2015	Calderari et al.

FOREIGN PATENT DOCUMENTS

WO	WO-2004045615	6/2004
WO	WO-2004067005	8/2004
WO	WO-2004703714	9/2004

OTHER PUBLICATIONS

Gaster, Laramie M. and King, Frank D., Serotonin 5-HT3 and 5-HT4 Receptor Antagonists, extracted from Medicinal Research Reviews, 1997 vol. 17, No. 2, pp. 163-214.

Tang, Jun et al., "Efficacy of RS-25259, a Novel 5-HT3 Antagonist, In the Prevention of Postoperative Nausea and Vomiting after Major Gynecologic Surgery," Anesthesiology, 1997, vol. 85, No. 3 suppl. p. A329.

Tang, Jun et al., The Efficacy of RS-25259, a Long-Acting Selective 5-HT3 Receptor Antagonist, for Preventing Postoperative Nausea and Vomiting After Hysterectomy Procedures, Anesthesia and Analgesia, 1998, vol. 87, pp. 462-467.

Adis R&D Profile, Palonosetron RS 25259 197, Drugs in R&D, Oct. 1999, vol. 2, No. 4, pp. 251-252.

Piraccini Gaia et al., An Interesting 5-HT3 Receptor Antagonist Antiemetic for Patients Undergoing Chemotheraphy-based Conditioning Regimens, Blood, Nov. 16, 2001, vol. 98, No. 11, part 2, p. 350b, abstract No. 5169.

Stacher, Georg, Palonosetron Helsinn, Current Opinion in Investigational Drugs. Oct. 2002, vol. 3, No. 10, pp. 1502-1507.

Navari, Rudolph M., Pathogenesis-Based Treatment of Chemotherapy-Induced Nausea and Vomiting—Two New Agents, Journal of Supportive Oncology, 2003, vol. 1(2), pp. 89-103.

Chaitow, 1990, 3 pages.

Opposition Brief filed by Dr. Reddy's Laboratories (UK) Limited, opposition to European Patent No. 1601359 B1 dated Jul. 7, 2009.

Photolytic and oxidative degradation of an antiemetic agent, RG 12915 (Won C. M. et al., International Journal of Pharmaceutics 121, 95-105 (1995).

Palonosetron: A phase II dose ranging study to assess over a 7 day period the single dose pharmacokinetic profile of palonosetron in patients receiving highly emetogenic chemotherapy. Piraccini et al., Proc. Am. Soc. Clin. Oncol 2002 21 Abs 449 (2002).

Formulation and administration techniques to minimize injection pain and tissue damage associated with parenteral products. Larry A. Gatlin and Carol A. Brister Gatlin, from Injectable Drug Development: Techniques to Reduce Pain and Irritation (Edited by Pramod K. Gupta and Gayle A. Brazeau; published by Informa Health Care) 1999; ISBN 1574910957, 9781574910957, p. 401-421.

Parenteral Dosage Forms. Joanne Broadhead, from Part 11-Early drug development, pharmaceutical preformulation and formulation: a practice guide from candidate drug selection to commercial dosage form (Edited by Mark Gibson; Published by Interpharma Press, 2001; ISBN 1574911201, 9781574911206), p. 331-353.

Opposition Brief filed by Tecnimede Sociedade Tecnico-Medicinal S.A. in opposition to European Patent No. 1601359 B1, Jul. 8, 2009.

Response brief filed by Helsinn Healthcare S.A. dated Jul. 13, 2007, in response to the communication pursuant to Art. 96(2) EPC of Jan. 3, 2007 regarding Serial No. 04 706 657.6-2123.

European Patent Office official communication dated Jul. 19, 2006, regarding Serial No. 04 706 657.6.

Response of Helsinn Healthcare S.A. dated Nov. 29, 2006, regarding EPO official communication date Jul. 19, 2006.

Lachman et al., The Theory and Practice of Industrial Pharmacy, 1986, third edition, pp. 652-784.

Declaration of Valentino J. Stella, Ph.D. dated Sep. 19, 2007.

Opposition Brief filed by Martin Paul White, opposition to European Patent No. 1601359 B1, Jul. 8, 2009.

Wong et al. (1995), in British Journal of Pharmacology, vol. 114, pp. 851-859.

Cover page and pp. 642-644 and 783-784 of The Theory and Practice of Industrial Pharmacy, Third Edition, Lea and Febiger (1986).

Cover page and pp. 514-515 of Modern Pharmaceutics, Second Edition, Marcel Dekker (1990).

Cover page and pp. 142-143 of Pharmaceutical Dosage Forms: Parenteral Medications vol. 1, Second Edition, Marcel Dekker (1992).

Mitsuo Matsumoto et al., "Yakuzaigaku Manual", 1st edition, Nanzando Co., Ltd. (1989) 2 pages.

Michael J. Pikal, "Freeze Drying", Encyclopedia of Pharmaceutical Technology, Third Edition, Jan. 2007, pp. 1824-1825, vol. 3, Informa Pharmaceuticals and Healthcare.

Daniele Bonadeo, "Supplemental Declaration of Daniele Bonadeo Under 37 C.F.R. 1.132", filed in U.S. Appl. No. 11/388,270, Jun. 8, 2009.

Kranke et al., 2007 "Recent advances, trends, and economic considerations in . . . " Expert Opinion Pharmacotherp., 8(18): 3217-3235.

Morrow et al., 1995, "Progress in reducing nausea and emesis: Comparisons of ondansetron, granisetron, and tropisetron." Cancer, vol. 76, No. 3 pp. 343-357.

USPTO Notice of Allowance and Fees Due, U.S. Appl. No. 11/388,270, filed Mar. 24, 2006, Date Mailed Jan. 26, 2010.

USPTO Office Action, U.S. Appl. No. 11/129,839, Date Mailed Jan. 15, 2010.

Israili, Zafar H., "Clinical Pharmacology of Serotonin Receptor Type (5-HT3) Antagonists," Curr. Med. Chem. Central Nervous System Agents, 2001:1, 171-199.

Barton (Citrate Buffer Calculation) 2000, 2 pages.

USPTO Office Action, U.S. Appl. No. 11/201,035, Date Mailed Aug. 19, 2009.

Response of Helsinn Healthcare to opposition of EP Serial No. 04 706 657.6, dated Feb. 11, 2010.

Annex 1 (Statement of Walso Mossi, Ph.D.) to Response of Helsinn Healthcare to Opposition of EP Serial No. 04 706 657.6 dated Feb. 11, 2010.

Annex 2 to Response of Helsinn Healthcare to Opposition of EP Serial No. 04 706 657.6 dated Feb. 11, 2010.

Annex 3 to Response of Helsinn Healthcare to Opposition of EP Serial No. 04 706 657.6 dated Feb. 11, 2010.

Summary of Product Characteristics for Aloxi 250 (2009).

Scientific Discussion from the European Public Assessment Report for Aloxi (Palonoseteron Hydrochloride) 2006.

6th Edition, Handbook of Pharmaceutical Excipients (2009), pp. 247-250 (RPS Publishing).

Lewis, Gareth A (2006) 'Optimization Methods,' Encyclopedia of Pharmaceutical Technology, 1:1, 2452-2467.

May 24, 2011 Para. IV notice from Teva Pharmaceuticals re '724 and '725 patents.

May 24, 2011 Para. IV notice from Sandoz re '724 and '725 patents.

May 24, 2011 Para. IV notice from Dr. Reddy's re '724 and '725 patents.

Aug. 9, 2011 Para. IV notice from Dr. Reddy's re '424 patent.

Aug. 19, 2011 Para. IV notice from Teva Pharmaceuticals re '424 patent.

Sep. 22, 2011 Para. IV notice from Sandoz re '724, '725 and '424 patents.

Jul. 8, 2011 Complaint for patent infringement (D. N.J. case No. 11-03962).

Sep. 23, 2011 Complaint for patent infringement (D. N.J. case No. 11-5579).

(56) **References Cited**

OTHER PUBLICATIONS

Aug. 31, 2011 Answer and counterclaim of Dr. Reddy's Laboratories, Ltd. and Dr. Reddy's Laboratories, Inc. (D. N.J. case No. 11-03962).
Sep. 13, 2011 Sandoz Inc.'s answer to complaint for patent infringement and counterclaims (D. N.J. case No. 11-03962).
Sep. 13, 2011 Teva Pharmaceuticals USA, Inc. and Teva Pharmaceutical Industries Ltd.'s answer (D. N.J. case No. 11-03962).
Oct. 5, 2011 Plaintiff's reply to answer and counterclaim of Dr. Reddy's Laboratories, Ltd. and Dr. Reddy Laboratories, Inc. (D. N.J. case No. 11-03962).
Oct. 21, 2011 Plaintiff's reply to Sandoz Inc.'s answer to complaint for patent infringement and counterclaims (D. N.J. case No. 11-03962).
Oct. 24, 2011 Answer and counterclaim of Dr. Reddy's Laboratories, Ltd. and Dr. Reddy's Laboratories, Inc. (D. N.J. case No. 11-5579).
Oct. 24, 2011 Sandoz Inc.'s answer to complaint for patent infringement and counterclaims (D. N.J. case No. 11-5579).
Oct. 27, 2011 Order consolidating the two cases (D. N.J. case No. 11-5579).
Nov. 17, 2011 Plaintiffs' reply to answer and counterclaim of Dr. Reddy's Laboratories, Ltd. and Dr. Reddy's Laboratories, Inc. (D. N.J. case No. 11-03962).
Nov. 17, 2011 Plaintiffs' reply to Sandoz Inc.'s answer to complaint for patent infringement and counterclaims (D. N.J. case No. 11-03962).
Dec. 5, 2011 Teva Pharmaceuticals USA Inc. and Teva Pharmaceuticals Industries Ltd.'s answer to complaint for patent infringement of the '424 patent (D. N.J. case No. 11-03962).
May 21, 2012 Defendants' opening claim construction brief (including exhibits 1-31).
May 21, 2012 Plaintiffs' opening claim construction brief (including exhibits 1-15).
Jul. 20, 2012 Defendants' responsive claim construction brief (including exhibits 1-3).
Jul. 20, 2012 Plaintiffs' responsive claim construction brief (including Exhibits A and B).
Sep. 7, 2012 Court transcript from Sep. 7, 2012 Markman hearing and Plaintiffs' PowerPoint presentation (D. N.J. case No. 11-03962).
Dec. 1, 2011 Sandoz Inc.'s invalidity contentions pursuant to L. Pat. R. 3.6(c) (D. N.J. case No. 11-03962).
Dec. 1, 2011 Teva Pharmaceuticals USA, Inc. and Teva Pharmaceutical Industries, Ltd.'s invalidity contentions, pursuant to L. Pat. R. 3.6(c)(D. N.J. case No. 11-03962).
Dec. 1, 2011 Dr. Reddy's Laboratories, Ltd.'s and Dr. Reddy's Laboratories, Inc.'s invalidity contentions pursuant to L. Pat. R. 3.6(c) (D. N.J. case No. 11-03962).
Jan. 31, 2012 Plaintiffs responses to defendants' invalidity contentions (D. N.J. case No. 11-03962).
Sep. 25, 2012 Sandoz Inc.'s first amended invalidity contentions pursuant to L. Pat. R. 3.6(c) (D. N.J. case No. 11-03962).
Nov. 19, 2012 Plaintiffs' responses to Sandoz Inc.'s first amended invalidity contentions (D. N.J. case No. 11-03962).
L.G. Wade Jr., Organic Chemistry, Ch. 19: Amines, pp. 867-936 (Prentice Hall 3d ed. 1995).
L. Lachman et al., The Theory and Practice of Industrial Pharmacy, pp. 642-644, 783-784 (Lea & Febiger 3d ed. 1986).
P.P. DeLuca et al., Formulation of Small Volume Parenterals in Pharmaceutical Dosage Forms: Parenteral Medications, vol. 1, Ch. 5, pp. 173-248 (Avis, Lieberman, Lachman eds., Marcel Dekker Inc. 2d ed. 1992).
C.M. Won et al, Photolytic and Oxidative Degradation of an Antiemetic Agent, RGI2915, Int'l J Pharmaceutics 121:95-105 (1995).
R.D. Clark et al., 2-(Quinuciidin-3-yl)pyrido-[4,3-b]indol-I-ones and Isoquinoin-I-ones. Potent Conformationally Restricted 5-HT3 Receptor Antagonists, J Med. Chem. 36:2645-57 (1993).
L.A. Trissel, Drug Stability and Compatibility Issues, Handbook on Injectable Drugs, pp. XI-XVI (ASHP 7th ed. 1992).
J. Broadhead, Parenteral Dosage Forms, Pharmaceutical Preformulation and Formulation: A Practical Guide from Candidate Drug Selection to Commercial Dosage Form, Ch. 9, pp. 331-354 (Gibson ed., CRC Press 1st ed. 2001).
K.A. Connors et al., Chemical Stability of Pharmaceuticals: A Handbook for Pharmacists (John Wiley & Sons 2d ed. 1986).
Zofran®, in The Physician's Desk Reference, op. 1503-07 (5th ed. 2001).
Anzemet®, in The Physician's Desk Reference, pp. 680-683 (5th ed. 2001).
Kytril®, in The Physician's Desk Reference, pp. 3104-3106 (5th ed. 2001).
L.A. Trissel, Ondansetron HCI, in Handbook on Injectable Drugs, pp. 683-688 (ASHP 7th ed. 1992).
Navoban® (tropisetron HCI) Malaysian Prescribing Information (Sep. 2000).
Kytril® (granisetron HCI) South African Prescribing Information (Dec. 1993).
S. Motola and S. Agharkar, Preformulation Research of Parenteral Medications, Pharmaceutical Dosage Forms: Parenteral Medications, vol. 1, Ch. 4, pp. 115-172 (Avis, Lieberman, Lachman eds., Marcel Dekker Inc. 2d ed. 1992).
J. Wells, Pharmaceutical Preformuatlion: The Physicochemical Properties of Drug Substances, Ch. 5: Drug Stability, pp. 152-191 (Ellis Horwod Ltd. 1988).
J. Swarbrick and Boylan, Encyclopedia of Pharmaceutical Technology, Excipients Chapter: Their Role in Parenteral Dosage Forms, vol. 19(2):137-172 (Marcel Dekker, Inc. 2000).
Handbook of Pharmaceutical Excipients, 3d Ed., (Kibbe ed. Pharmaceutical Press 2000); pp. 140-143, 191-194, 324-238.
G. Stacher, Palonosetron (Helsinn), Curro. Opin. Investig. Drugs, 3(10) 1502-7 (2002).
Handbook of Modern Pharmaceutical Analysis, (S. Ahuja et al. ed., Academic Press, 2001).
Jun. 8, 2009 Bonadeo Declaration.
Jun. 8, 2009 Bonadeo Declaration, Exhibit 2.
Jun. 8, 2009 Bonadeo Declaration, Exhibit 3.
HELSN0117262-69 (2008).
HELSN0117270-312 (2012).
Feb. 13, 2007 Statutory Declaration of Daniele Bonadeo, with Exhibit A.
Nov. 21, 2007 Statutory Declaration of Giorgio Calderari, Daniele Bonadeo, Roberta Cannella, Enrico Braglia, and Riccardo Braglia.
Reddy's Paragraph IV notice regarding all three patents (D. N.J. Case No. 12-2867), dated Mar. 30, 2012.
May 11, 2012 Complaint for patent infringement filed by Helsinn and Roche (D. N.J. Case No. 12-2867).
Jun. 26, 2012 Notice of Reddy's motion to dismiss (D. N.J. Case. No. 12-2867).
Jun. 26, 2012 Dr. Reddy's Laboratories, Ltd.'s and Dr. Reddy's Laboratories, Inc.'s memorandum of law in support of their motion to dismiss or for summary judgment of non-infringement of U.S. Pat. No. 7,947,724 (D. N.J. Case No. 12-2867) (including Exhibits 1-10).
Aug. 16, 2012 Notice of Plaintiffs' cross-motion for partial summary judgment of infringement (D. N.J. Case No. 12-2867).
Aug. 6, 2012 Plaintiffs' opposition to Defendants' motion to dismiss or for summary judgment of noninfringement and cross-motion for partial summary judgment of infringement (D. N.J. Case No. 12-1867) (including exhibits 1-4).
Schöneich declaration (D. N.J. Case No. 12-2867) (Including Exhibits A and 1-24), dated Aug. 6, 2012.
Sep. 4, 2012 Reddy's brief in opposition to Plaintiffs' cross-motion for partial summary judgment and reply memorandum of law in further support of Reddy's motion to dismiss or for summary judgment of non-infringement (D. N.J. Case No. 12-2867)(Including Exhibits 1-4).
DeLuca Declaration (D. N.J. Case No. 12-2867)(Including exhibits A-J), dated Sep. 3, 2012.
Sep. 10, 2012 Plaintiffs' letter to Judge Cooper in response to Reddy's combined opposition to Plaintiffs' cross-motion for partial summary judgment and reply in support of Reddy's motion to dismiss or for summary judgment of noninfringement (D. N.J. Case No. 12-2867)(including exhibits A and B).

(56) **References Cited**

OTHER PUBLICATIONS

Sep. 14, 2012 Dr. Reddy's letter in response to Plaintiffs' Sep. 10, 2012 letter (D. N.J. Case No. 12-2867).
USPTO Office Action, U.S. Appl. No. 11/388,268, filed Mar. 24, 2006, Mail Date Mar. 29, 2010.
USPTO Non-Final Office Action, U.S. Appl. No. 11/186,311, mailed Aug. 30, 2006.
USPTO Non-Final Office Action, U.S. Appl. No. 11/186,311, mailed Oct. 5, 2007.
USPTO Non-Final Office Action, U.S. Appl. No. 11/186,311, mailed Oct. 6, 2008.
USPTO Final Office Action, U.S. Appl. No. 11/186,311, mailed May 20, 2009.
USPTO Advisory Action, U.S. Appl. No. 11/186,311, mailed Jul. 15, 2009.
USPTO Notice of Allowance and Fees Due, U.S. Appl. No. 11/186,311, mailed Mar. 4, 2011.
USPTO Notice of Allowability, U.S. Appl. No. 11/186,311, dated May 24, 2011.
USPTO Non-Final Office Action, U.S. Appl. No. 11/388,268, mailed Jul. 17, 2006.
USPTO Non-Final Office Action, U.S. Appl. No. 11/388,268, mailed Nov. 17, 2006.
USPTO Non-Final Office Action, U.S. Appl. No. 11/388,268, mailed Oct. 3, 2007.
USPTO Non-Final Office Action, U.S. Appl. No. 11/388,268, mailed Mar. 26, 2008.
USPTO Final Office Action, U.S. Appl. No. 11/388,268, mailed Nov. 12, 2008.
USPTO Non-Final Office Action, U.S. Appl. No. 11/388,268, mailed Jul. 15, 2009.
USPTO Notice of Allowance and Fees Due, U.S. Appl. No. 11/388,268, mailed Dec. 22, 2010.
USPTO Non-Final Office Action, U.S. Appl. No. 11/388,269, mailed Jul. 19, 2006.
USPTO Non-Final Office Action, U.S. Appl. No. 11/388,269, mailed Nov. 17, 2006.
USPTO Non-Final Office Action, U.S. Appl. No. 11/388,269, mailed Sep. 20, 2007.
USPTO Non-Final Office Action, U.S. Appl. No. 11/388,269, mailed Jul. 9, 2008.
USPTO Interview Summary, U.S. Appl. No. 11/388,269, dated Apr. 28, 2009.
USPTO Final Office Action, U.S. Appl. No. 11/388,269, mailed May 20, 2009.
USPTO Advisory Action, U.S. Appl. No. 11/388,269, mailed Jul. 15, 2009.
USPTO Notice of Abandonment, U.S. Appl. No. 11/388,269, mailed Dec. 18, 2009.
USPTO Non-Final Office Action, U.S. Appl. No. 11/388,270, mailed Jul. 13, 2006.
USPTO Interview Summary, U.S. Appl. No. 11/388,270, dated Aug. 3, 2006.
USPTO Non-Final Office Action, U.S. Appl. No. 11/388,270, mailed Nov. 16, 2006.
USPTO Non-Final Office Action, U.S. Appl. No. 11/388,270, mailed Sep. 20, 2007.
USPTO Interview Summary, U.S. Appl. No. 11/388,270, dated Dec. 14, 2007.
USPTO Non-Final Office Action, U.S. Appl. No. 11/388,270, mailed Mar. 25, 2008.
USPTO Final Office Action, U.S. Appl. No. 11/388,270, mailed Oct. 29, 2008.
USPTO Advisory Action, U.S. Appl. No. 11/388,270, mailed Jan. 23, 2009.
USPTO Non-Final Office Action, U.S. Appl. No. 11/388,270, mailed Jul. 9, 2009.
USPTO Interview Summary, U.S. Appl. No. 11/388,270, dated Nov. 12, 2010.
USPTO Notice of Allowance and Fees Due, U.S. Appl. No. 11/388,270, mailed Jan. 5, 2011.
USPTO Non-Final Office Action, U.S. Appl. No. 13/087,012, mailed Mar. 12, 2012.
USPTO Non-Final Office Action, U.S. Appl. No. 13/087,012, mailed Jul. 19, 2012.
USPTO Interview Summary, U.S. Appl. No. 13/087,012, dated Feb. 15, 2013.
USPTO Notice of Allowance and Fees Due, U.S. Appl. No. 13/087,012, mailed Feb. 27, 2013.
USPTO Response to Amendment under Rule 312, U.S. Appl. No. 13/087,012, mailed Apr. 4, 2013.
USPTO Non-Final Office Action, U.S. Appl. No. 11/129,839, mailed Jun. 10, 2008.
Eisenberg et al. 2004, "Efficacy, safety and pharmacokinetics of palonosetron in patients receiving highly emetogenic cisplatin-based chemotherapy: a dose-ranging clinical study." Annals of Oncology, vol. 15, pp. 330-337.
Mayron et al. 1996, "Stability and compatibility of granistron hydrochloride in i.v. solutions and oral liquids and during simulated Y-site injection with selected drugs." Am J Health-Sys Pharm, 53: 294-304.
Trissel et al. 1997, "Compatibility of granisetron hydrochloride with selected drugs during simulated Y-site administration." Am J Health-Syst Pharm 54: 56-60.
USPTO Final Office Action, U.S. Appl. No. 11/129,839, mailed Mar. 17, 2009.
USPTO Advisory Action, U.S. Appl. No. 11/129,839, mailed Jul. 22, 2009.
USPTO Non-Final Office Action, U.S. Appl. No. 11/129,839, mailed Jan. 15, 2010.
USPTO Examiner Interview Summary, U.S. Appl. No. 11/129,839, mailed Nov. 9, 2010.
USPTO Notice of Allowance and Fees Due, U.S. Appl. No. 11/129,839, mailed Jan. 3, 2011.
USPTO Notice of Abandonment, U.S. Appl. No. 11/129,839, mailed Apr. 18, 2011.
USPTO Non-Final Office Action, U.S. Appl. No. 13/077,374, mailed Feb. 17, 2012.
Roila et al. 1998, "Prevention of chemotherapy- and radiotherapy-induced emesis: Results of the Perugia consensus conference." Annals of Oncology, vol. 9, pp. 811-819.
USPTO Final Office Action, U.S. Appl. No. 13/077,374, mailed Nov. 23, 2012.
Piraccini, Gaia et al., American Society of Clinical Oncology May 12-15, 2001 San Francisco—USA (vol. 20, part 1 of 2, 2001) (Abstract No. 1595).
USPTO Non-Final Office Action, U.S. Appl. No. 11/201,035, mailed May 16, 2008.
USPTO Final Office Action, U.S. Appl. No. 11/201,035, mailed Feb. 4, 2009.
USPTO Final Office Action, U.S. Appl. No. 11/201,035, mailed Jun. 8, 2010.
FDA approval letter of Aloxi (palonosetron hydrochloride injection), dated Jul. 25, 2003.
Macciocchi A, Chernoff SB, Gallagher SC. A phase II dose-ranging study to assess intravenous doses of palonosetron for the prevention of highly emetogenic chemotherapy-induced nausea and vomiting. In: Program/Proceedings of the 38th Annual Meeting of the American Society of Clinical Oncology; May 18-21, 2002; Orlando, Fla. Abstract 1480.
Grunberg SM, Hajdenberg J, Charu V, et al. Palonosetron is active in preventing acute and delayed emesis following moderately emetogenic chemotherapy: results of a phase III trial. Support Care Cancer 2002;10:Abstract P-113.
Aapro MS, Selak E, Lichinitser M, et al. Palonosetron is more effective than ondansetron in preventing chemotherapy-induced nausea and vomiting in patients receiving moderately emetogenic chemotherapy: results of a phase III trial. In: Program/Proceedings of the 39th Annual Meeting of the American Society of Clinical Oncology; May 31-Jun. 3, 2003; Chicago, Ill. Abstract 2918.
Aapro MS, Bertoli L, Lordick F, et al. Palonosetron is effective in preventing acute and delayed chemotherapy induced nausea and vomiting in patients receiving highly emetogenic chemotherapy. 15th

(56) **References Cited**

OTHER PUBLICATIONS

MASCC International Symposium, Berlin, Germany. Support Care Cancer, vol. 11, No. 6, Jun. 2003, A17.
Cartmell AD, Ferguson S, Yanagihara R, et al. Protection against chemotherapy-induced nausea and vomiting is maintained over multiple cycles of moderately or highly emetogenic chemotherapy by palonosetron, a potent 5 HT3 receptor antagonist. In: Program/Proceedings of the 39th Annual Meeting of the American Society of Clinical Oncology; May 31-Jun. 3, 2003; Chicago, Ill. Abstract 3041.
Sabra, Choice of a 5-HT3 Receptor Antagonist for the Hospital Formulary, EHP, Oct. 1996, vol. 2, Supp 1, S19-S24.
Gregory and Ettinger, 5HT3 receptor antagonists for the prevention of chemotherapy-induced nausea and vomiting. A comparison of their pharmacology and clinical efficacy. Drugs, Feb. 1998; 55(2): 173-189.
Full Prescribing Information for Aloxi (palonosetron HCI) injection for Intravenous Use (2008).
Drug, Dose & Schedule Recommendations for Antiemetic Regimens (American Society for Clinical Oncology) (2006).
Yamakuni, et al., The Journal of Pharmacology and Experimental Therapeutics, Probable Involvement of the 5-Hydroxytryptamine4 Receptor in Methotrexate-Induced Delayed Emesis in Dogs, 2000, The American Society for Pharmacology and Experimental Therapeutics, vol. 292, No. 3, p. 1002-1294.
Geling, et al., Should 5-Hydroxytryptamine-3 Receptor Antagonists Be Administered Beyond 24 Hours After Chemotherapy to Prevent Delayed Emesis? Systematic Re-Evaluation of Clinical Evidence and Drug Cost Implications, Journal of Clinical Oncology, vol. 23, No. 6, Feb. 20, 2005 (American Society of Clinical Oncology), pp. 1289-1294.
Rojas, et al., International Anesthesia Research Society, Palonosetron Exhibits Unique Molecular Interactions with 5-HT3 Receptor, vol. 107, No. 2, Aug. 2008, p. 469-478.
Rojas, et al., Palonosetron triggers 5-HT3 receptor internalization and causes inhibition of receptor function, European Journal of Pharmacology 626 (2010), p. 193-199.
Regan-Shaw, et al., Dose translation from animal to human studies revisited, The FASEB Journal, Life Sciences Forum, p. 659-661.
Saito, et al., Palonosetron plus dexamethasone versus granisetron plus dexamethasone for prevention of anusea and vomiting during chemotherapy: a double-blind, double-dummy, randomised, comparative phased III trial, www.thelancet.com/oncology, vol. 10, Feb. 2009, p. 115-124.
Palonosetron: more than just another option?. www.thelancet.com/oncology, vol. 10, Feb. 2009, p. 100-101.
Lorusso, et al., Single dose of palonosetron plus dexamethasone to control nausea, vomiting and to warrant an adequate food intake in patients treated with highly emetogenic chemotherapy (HEC). Preliminary results, Support Care Cancer, published online Mar. 18, 2009.
Grunberg, et al., Effectiveness of a single-day three-drug regimen of dexamethasone, palonosetron, and aprepitant for the prevention of acute and delayed nausea and vomiting caused by moderately emetogenic chemotherapy, Support Care Cancer (2009) 17:589-594.
Celio, et al., Clinical update on palonosetron in the management of chemotherapy-induced nausea and vomiting, Tumor, 94: 447-452, 2008.
Ellebaek, et al., Optimizing antiemetic therapy in multiple-day and multiple cycles of chemotherapy, Lippincott williams & Wilkins, Current Opinion in Supportive and Palliative Care, 2008, 2:28-34.
Herrington, et al., Randomized, Placebo-controlled, Pilot Study Evaluating Aprepitant Single Dose Plus Palonosetron and Dexamethasone for the Prevention of Acute and Delayed Chemotherapy-induced Nausea and Vomiting, American Cancer Society, published online Mar. 7, 2008 in Wiley InterScience (www.interscience.wiley.com).
Massa, et al., Palonosetron plus dexamethasone effectively prevents acute and delayed chemotherapy-induced nausea and vomiting following highly or moderately emetogenic chemotherapy in pretreated patients who have failed to respond to a previous antiemetic treatment: Comparison between elderly and non-elderly patient response, Critical Reviews in Oncology/Hematology 70 (2009) 83-91.
2006 Update of the ASCO Recommendations for Antiemetics in Oncology: Guideline Summary, American Cancer Society of Clinical Oncology, Jul. 2006, www.jopasco.org.
Warr, David, Standard treatment of chemotherapy-induced emesis, Support Care Cancer, vol. 5, pp. 12-16, 1997.
Aapro, M.S., et al. A phase III, double-blind, randomized trial of palonosetron compared with ondansetron in preventing chemotherapy-induced nausea and vomiting following highly emetogenic chemotherapy. Annals of Oncology, vol. 17, pp. 1441-1449, 2006.
Eisenberg, Peter, et al. Improved Prevention of Moderately Emetogenic Chemotherapy-Induced Nausea and Vomiting with Palonosetron, a Pharmacologically Novel5-HT3 Receptor Antagonist. Cancer, vol. 98, No. 11, pp. 2473-2482, Dec. 1, 2003.
Gandara, D.R., et al. The delayed-emesis syndrome from cisplatin: Phase III evaluation of ondansetron versus placebo. Semin Oneal vol. 19, No. 4, pp. 67-71, Aug. 1992 (suppl 10).
Goedhals, L., et al. Control of delayed nausea and vomiting with granisetron plus dexamethasone or dexamethasone alone in patients receiving highly emetogenic chemotherapy: A double-blind, placebo-controlled, comparative study. Ann Oneal, vol. 9, pp. 661-666, 1998.
Gralla, R., et al. Palonosetron improves prevention of chemotherapy-induced nausea and vomiting following moderately emetogenic chemotherapy: results of a double-blind randomized phase III trial comparing single doses of palonosetron with ondansetron. Annals of Oncology, vol. 14, pp. 1570-1577, 2003.
Italian Group for Antiemetic Research. Dexamethasone alone or in combination with ondansetron for the prevention of delayed nausea and vomiting induced by chemotherapy. N Engl J Med, vol. 342, No. 21, pp. 1554-1559, May 25, 2000.
Kaizer, L., et al. Effect of schedule and maintenance on the antiemetic efficacy of ondansetron combined with dexamethasone in acute and delayed nausea and emesis in patients receiving moderately emetogenic chemotherapy: A phase III trial by the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol, vol. 12, No. 5, pp. 1050-1057, May 1994.
Latreille, J., et al. Use of dexamethasone and granisetron in the control of delayed emesis for patients who receive highly emetogenic chemotherapy: National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol, vol. 16, No. 3, pp. 1174-1178, Mar. 1998.
Antiemetic Subcommittee of the Multinational Association of Supportive Care in Cancer (MCSCC). Prevention of chemotherapy- and radiotherapy-induced emesis: Results of the Perugia Consensus Conference. Annals of Oncology, vol. 9, pp. 811-819, 1998.
Moyer, Paula. New Understanding of Emesis Pathways Leading to New Treatment, Better Control. Oncology Times, vol. 25, Issue 10, pp. 48-51, May 25, 2003.
Navari, R.M., et al. Oral ondansetron for the control of cisplatin-induced delayed emesis: A large, multicenter, double-blind, randomized comparative trial of ondansetron versus placebo. J Clin Oncol, vol. 13, No. 9, pp. 2408-2416, Sep. 1995.
Olver, I., et al. A multicenter, double-blind study comparing placebo, ondansetron and ondansetron plus dexamethasone for the control of cisplatin-induced delayed emesis. Ann Oncol, vol. 7, pp. 945-952, 1996.
Pater, J.L., et al. The role of the 5-HT3 antagonists ondansetron and dolasetron in the control of delayed onset nausea and vomiting in patients receiving moderately emetogenic chemotherapy. Ann Oncol, vol. 8, pp. 181-185, 1997.
Rojas, Camilo, et al. The Antiemetic 5-HT3 Receptor Antagonist Palonosetron Inhibits Substance P-Mediated Responses in Vitro and in Vivo. J Pharmacal Exper Thera, vol. 335, No. 2, pp. 362-368, 2010.
Sorbe, B. G., et al. A study evaluating the efficacy and tolerability of tropisetron in combination with dexamethasone in the prevention of delayed platinum-induced nausea and emesis. Cancer, vol. 83, pp. 1022-1032, 1998.
Stewart, A., et al. Ondansetron Compared with Granisetron in the Prophylaxis of Cyclophosphamide-Induced Emesis in Out-Patients: A Multicentre, Double-Blind, Double-Dummy, Randomised, Parallel-Group Study. Oncology, vol. 52, pp. 202-210, 1995.

(56) **References Cited**

OTHER PUBLICATIONS

Weiderpass, Elisabete, et al. Use of an NK1 Receptor Antagonist to Prevent Delayed Emesis After Cisplatin. Journal of the National Cancer Institute, vol. 89, No. 11, pp. 817-818, Jun. 4, 1997.
Akers, Michael J., Excipient-Drug Interactions in Parenteral Formulations. Journal of Pharmaceutical Sciences, vol. 91, No. 11, Nov. 2002, pp. 2283-2300.
Maemondo, et al., A phase II study of palonosetron combined with dexamethasone to prevent nausea and vomiting induced by highly emetogenic chemotherapy. Annals of Oncology, Nov. 2009, vol. 20, No. II, pp. 1860-1866.
Program/Proceedings American Society of Clinical Oncology, vol. 20, Part 1 of 2, 2001, Abstract No. 1595 and associated poster presentation.
Saito, et al., Review of palonosetron: emerging data distinguishing it as a novel 5-HT3 receptor antagonist for chemotherapy-induced nausea and vomiting. Expert Opin. Pharmacother (2010) II (6), pp. 1003-1014.
MGI-HHC_SEC_filing (2001).
ROCHE0008749-876 (1995) (portions redacted).
HELSNO135068-82 (1998) (portions redacted).
English-language translation of Italian-language portions of HELSNO135068-82 (1998).
HELSN0161327-348 (2000) (portions redacted).
HELSN0138407-24 (1998) (portions redacted).
HELSN0376401-469 (2002) (portions redacted).
HELSN0392650-72 (1999) (portions redacted).
Dr. Reddy's Labs., Ltd.'s and Dr. Reddy's Labs., Inc.'s Memorandum of Law in Support of Their Motion to Amend Their Invalidity Contentions dated Feb. 15, 2013 (D.N.J. Case No. 11-3962).
HELSN0376719-21 (2001).
HELSN0376722-23 (2001).
HELSN0376724 (2002).
Dr. Reddy's Laboratories, Ltd.'s and Dr. Reddy's Laboratories, Inc.'s Redline of Proposed Amended Invalidity Contentions Pursuant to L. Pat. R. 3.6(c) filed Feb. 15, 2013 (D.N.J. Case No. 11-3962).
Dr. Reddy's Laboratories, Ltd.'s and Dr. Reddy's Laboratories, Inc.'s Reply Memorandum of Law in Further Support of Their Motion to Amend Their Invalidity Contentions dated Mar. 15, 2013 (D.N.J. Case No. 11-3962).
Teva Pharm. Indus., Ltd.'s and Teva Pharm. USA, Inc.'s Memorandum in Support of Their Motion to Amend Invalidity Contentions dated Feb. 15, 2013 (D.N.J. Case No. 1-3962).
HELSN0388553-65 (1998).
HELSN0388566-68 (1998).
HELSN0388569-74 (1998).
HELSN0388587-91 (1998).
HELSN0388592-95 (1998).
English-language translation of HELSN0388592-95 (1998).
HELSN0388596-97 (1998).
HELSN0388604 (1998).
HELSN0388605-06 (1998).
HELSN0388607-09 (1998).
HELSN0389134-44 (1999).
HELSN0389145-48 (1999).
HELSN0389149-61 (2000).
HELSN0392047-48 (1998).
HELSN0392393-94 (1998).
HELS0393657-61 (2000).
English-language translation of Italian-language portions of HELSN039657-61 (2000).
Excerpts from Calderari Deposition Transcript, pp. 1-4, 229-232, and 278-393 (2013).
HELSN0000093-9 (2006).
HELSN0004207 (2002).
HELSN0004217 (2002).
Teva Pharm. Indus., Ltd.'s and Teva Pharm. USA, Inc.'s Reply in Support of Their Motion to Amend Their Invalidity Contentions dated Mar. 15, 2013 (D.N.J. Case No. 1-3962).
HELSN00388448-542 (1998-1999).
English-language translation of Italian-language portions of HELSN00388448-542 (1998-1999).
HELSN0388543-44 (1999).
HELSN0388545-52 (1998).
HELSN0388575-76 (1998).
HELSN0388577-80 (1998).
HELSN0388581-82 (1998).
HELSN0388583-84 (1998).
HELSN0388585 (1998).
HELSN0388586 (1998).
HELSN0388598-601 (1998).
HELSN0388602-03 (1998).
HELSN0388610 (1998).
Sandoz Inc.'s Redacted Memorandum of Law in Support of its Motion to Amend its Invalidity Contentions dated Feb. 15, 2013 (D.N.J. Case No. 11-3962).
Exhibit G to Sandoz Inc.'s Redacted Memorandum of Law in Support of its Motion to Amend its Invalidity Contentions dated Feb. 15, 2013 (D.N.J. Case No. 11-3962).
Sandoz Inc.'s Redacted Reply Memorandum of Law in Support of its Motion to Amend its Invalidity Contentions dated Mar. 15, 2013 (D.N.J. Case No. 11-3962).
Aurobindo Pharma Ltd. Paragraph IV notice regarding U.S. Pat. Nos. 7,947,724; 7,947,725; and 7,960,424, dated Mar. 5, 2013 (D. Del. Case No. 13-688).
Complaint for patent infringement filed by Helsinn Healthcare S.A. and Roche Palo Alto LLC against Aurobindo Pharma Ltd. and Aurobindo Pharma USA Inc. dated Apr. 16, 2013 (D. Del. Case No. 13-688).
Accord Healthcare, Inc. Paragraph IV notice regarding U.S. Pat. Nos. 7,947,724; 7,947,725; and 7,960,424, dated Apr. 3, 2013.
Drug Marketing Approval Document for Aloxi I.V. DRip Infusion Bag 0.75 mg, Japanese Ministry of Health, Labour and Welfare (2012).
English-language translation of Cite No. 800 (2012).
Approval of Partial Changes in Drug Marketing Approved Items for Aloxi I.V. Drip Infusion Bag 0.75 mg, Japanese Ministry of Health, Labour and Welfare (2012).
English language translation of Cite No. 902 (2012).
Amendment and Response, U.S. Appl. No. 13/902,132, dated Oct. 9, 2013 (Exhibit 1039 of IPR2015-01550, -01151, -01553, -01554).
Amendment After Final, U.S. Appl. No. 13/902,132, dated Feb. 21, 2014 (Exhibit 1009 of IPR2015-01550, -01151, -01553, -01554).
USPTO Non-Final Office Action, U.S. Appl. No. 14/597,489, mailed Feb. 26, 2015.
USPTO Final Office Action, U.S. Appl. No. 14/070,981, mailed Jun. 16, 2015.
Dr. Reddy's Laboratories, Ltd.'s and Dr. Reddy's Laboratories, Inc.'s Second Amended Invalidity Contentions Pursuant to L. Pat. R. 3.6(c) dated Mar. 12, 2015 (D.N.J. 11-3962, consolidated).
Opening Expert Report of Edward P. Gelmann, M.D., dated Jun. 24, 2015 (D. Del. 13-688, consolidated).
Opening Expert Report of James E. Kipp, Ph.D., dated Jun. 24, 2015 (D. Del. 13-688, consolidated).
Opening Expert Report of Max Talbott, Ph.D., dated Jun. 24, 2015 (D. Del. 13-688, consolidated).
Affirmative Expert Report of Elizabeth M. Topp, Ph.D., dated Jun. 24, 2015 (D. Del. 13-688, consolidated).
Dr. Reddy's Laboratories, Ltd. and Dr. Reddy's Laboratories, Inc. Petition for Inter Partes Review of U.S. Pat. No. 8,729,094 dated Jul. 3, 2015 (IPR2015-01550).
Dr. Reddy's Laboratories, Ltd. and Dr. Reddy's Laboratories, Inc. Petition for Inter Partes Review of U.S. Pat. No. 8,729,094 dated Jul. 3, 2015 (IPR2015-01551).
Dr. Reddy's Laboratories, Ltd. and Dr. Reddy's Laboratories, Inc. Petition for Inter Partes Review of U.S. Pat. No. 8,729,094 dated Jul. 3, 2015 (IPR2015-01553).
Dr. Reddy's Laboratories, Ltd. and Dr. Reddy's Laboratories, Inc. Petition for Inter Partes Review of U.S. Pat. No. 8,729,094 dated Jul. 3, 2015 (IPR2015-01554).
Exhibit 1021 to Dr. Reddy's Laboratories, Ltd. and Dr. Reddy's Laboratories, Inc. Petitions for Inter Partes Review of U.S. Pat. No.

(56) **References Cited**

OTHER PUBLICATIONS

8,729,094, Declaration of William P. McGuire, Ph.D., dated Jul. 2, 2015 (IPR2015-01550, -01151, -01553, -01554).
Exhibit 1023 to Dr. Reddy's Laboratories, Ltd. and Dr. Reddy's Laboratories, Inc. Petitions for Inter Partes Review of U.S. Pat. No. 8,729,094, Declaration of David G. Frame, Pharm.D., dated Jul. 1, 2015 (IPR2015-01550, -01151, -01553, -01554).
Exhibit 1040 to Dr. Reddy's Laboratories, Ltd. and Dr. Reddy's Laboratories, Inc. Petitions for Inter Partes Review of U.S. Pat. No. 8,729,094, Declaration of Dr. Patrick P. DeLuca dated Jul. 1, 2015 (IPR2015- 01550, -01151, -01553, -01554).
R. J. Gralla, et al., "Recommendations for the Use of Antiemetics: Evidence-Based, Clinical Practice Guidelines," *J. Clin. Oncol.* 17(9):2971-94 (1999) (Exhibit 1013 of IPR2015-01550, -01151, -01553, -01554).
L. P. Cohen, "Many Medicines Prove Potent for Years Past Their Expiration Dates," *Wall St. J.*, Mar. 28, 2000 (Exhibit 1020 of IPR2015-01550, -01151, -01553, -01554).
D. R. Gandara, et al., "Consensus Proposal for 5HT3 Antagonists in the Prevention of Acute Emesis Related to Highly Emetogenic Chemotherapy: Dose, Schedule, and Route of Administration," *Support Care Cancer* 6:237-243 (1998) (Exhibit 1027 of IPR2015-01550, -01151, -01553, -01554).
U.S. Food and Drug Administration, Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research, "Estimating the Safe Starting Dose in Clinical Trials for Therapeutics in Adult Healthy Volunteers," Draft Guidance, Dec. 2002 (Exhibit 1031 of IPR2015-01550, -01151, -01553, -01554).
"Helsinn & MGI Pharma Announce Completion of Pivotal Phase 3 Trials of Palonosetron," 2002 (Exhibit 1033 of IPR2015-01550, -01151, -01553, -01554).
"Helsinn Healthcare Announce the Completion of Patient Enrollment for First Palonosetron Phase 3 Pivotal Trial," 2001 (Exhibit 1034 of IPR2015-01550, -01151, -01553, -01554).
"MGI Pharma Sign Exclusive License Agreement with Helsinn Healthcare SA, for Palonosetron, a Phase 3 Anti-emetic," 2001 (Exhibit 1035 of IPR2015-01550, -01151, -01553, -01554).
G. W. Brown, et al., "The Effectiveness of a Single Intravenous Dose of Ondansetron," *Oncology* 49:273-278 (1992) (Exhibit 1044 of IPR2015-01550, -01151, -01553, -01554).
Helsinn Healthcare S.A. v. *Dr. Reddy's Laboratories, Ltd.*, Claim Construction Order, dated Feb. 19, 2015 (D.N.J. 12-2867) (Exhibit 1045 of IPR2015-01550, -01151, -01553, -01554).
K. Mikawa, et al., "Optimal Dose of Granisetron for Prophylaxis Against Postoperative Emesis after Gynecological Surgery," *Anesth Analg* 85:652-6 (1997) (Exhibit 1049 of IPR2015-01550, -01151, -01553, -01554).
Pharmaceutical Dosage Forms: Parenteral Medications, vol. 1, pp. 17-25, 115-116, 140-143, 150-151, 173-175, 190-203, 207-212 (Avis, Lieberman, Lachman eds., Marcel Dekker Inc. 2d ed. 1992) (Exhibit 1050 of IPR2015-01550, -01151, -01553, -01554).
Exhibit 1053 to Dr. Reddy's Laboratories, Ltd. and Dr. Reddy's Laboratories, Inc. Petitions for Inter Partes Review of U.S. Pat. No. 8,729,094, Dose response curves for Chelly 1996 Exh. 1012 and Tang 1998 Exh. 1019.
Kytril amended label, Aug. 16, 2002 (Exhibit 1054 of IPR2015-01550, -01151, -01553, -01554).
USPTO Notice of Allowance and Fees Due, U.S. Appl. No. 13/087,012, mailed Jul. 3, 2013.
USPTO Non-Final Office Action and Examiner-Initiated Interview Summary, U.S. Appl. No. 13/901,437, mailed Jul. 29, 2013.
USPTO Non-Final Office Action, U.S. Appl. No. 13/902,132, mailed Aug. 8, 2013.
USPTO Interview Summary, U.S. Appl. No. 13/087,012 dated Jun. 13, 2013.
USPTO Notice of Allowance and Fees Due and Examiner-Initiated Interview Summary, U.S. Appl. No. 13/901,288, mailed Sep. 6, 2013.
CDER Approval Package for NDA 21-372, Clinical Pharmacology and Biopharmaceutics Review (2002).
USPTO Non-Final Office Action and Applicant-Initiated Interview Summary, U.S. Appl. No. 13/900,174, mailed Nov. 19, 2013.
USPTO Non-Final Office Action, U.S. Appl. No. 14/184,305, mailed May 29, 2014.
USPTO Applicant-Initiated Interview Summary, U.S. Appl. No. 14/184,305, dated Jul. 18, 2014.
USPTO Non-Final Office Action, U.S. Appl. No. 13/902,299, mailed Dec. 5, 2013.
USPTO Final Office Action, U.S. Appl. No. 13/902,132, mailed Dec. 6, 2013.
USPTO Non-Final Office Action, U.S. Appl. No. 14/052,925, dated Dec. 4, 2013.
USPTO Non-Final Office Action, U.S. Appl. No. 14/070,981, mailed Nov. 4, 2014.
Defendants Aurobindo Pharma Ltd.'s and Aurobindo Pharma USA Inc.'s Answer, Affirmative Defenses, and Counterclaims, dated Aug. 23, 2013 (D. Del. Case No. 13-688).
Plaintiff's Answer to the Counterclaims of Aurobindo Pharma USA Inc. and Aurobindo Pharma Ltd., dated Sep. 13, 2013 (D. Del. Case No. 13-688).
Plaintiffs' Responses to Dr. Reddy's Laboratories, Ltd. and Dr. Reddy's Laboratories, Inc.'s Amended Invalidity Contentions, dated Aug. 19, 2013 (D. N.J. Case Nos. 11-3962 and 11-5579; consolidated).
Plaintiffs' Responses to Sandoz Inc.'s Second Amended Invalidity Contentions, dated Aug. 19, 2013 (D. N.J. Case Nos. 11-3962 and 11-5579; consolidated).
Plaintiffs' Responses to Teva Pharmaceuticals USA, Inc. and Teva Pharmaceutical Industries, Ltd.'s First Amended Invalidity Contentions, dated Aug. 19, 2013 (D. N.J. Case Nos. 11-3962 and 11-5579; consolidated).
Complaint for patent infringement filed by Helsinn Healthcare SA and Roche Palo Alto LLC against Dr. Reddy's Laboratories, Ltd., Dr. Reddy's Laboratories, Inc., Sandoz Inc., Teva Pharmaceuticals USA, Inc., and Teva Pharmaceutical Industries, Ltd. regarding U.S. Pat. No. 8,518,981 dated Sep. 30, 2013 (D.N.J. Case No. (13-5815)).
Answer and Counterclaim of Dr. Reddy's Laboratories, Ltd. and Dr. Reddy's Laboratories, Inc. to Amended Complaint for Patent Infringement regarding U.S. Pat. Nos. 8,518,981, 8,598,218, and 8,598,219, dated Feb. 3, 2014 (D.N.J. Case No. 13-5815).
Sandoz Inc.'s Answer, Affirmative Defenses, and Counterclaims to Amended Complaint regarding U.S. Pat. Nos. 8,518,981, 8,598,218, and 8,598,219, dated Feb. 3, 2014 (D.N.J. Case No. 13-5815).
Defendants Teva Pharmaceuticals USA, Inc. and Teva Pharmaceutical Industries Ltd.'s Answer to Amended Complaint for Patent Infringement regarding U.S. Pat. Nos. 8,518,981, 8,598,218, and 8,598,219, dated Feb. 3, 2014 (D.N.J. Case No. 13-5815).
Teva Pharmaceuticals USA, Inc Paragraph IV Letter regarding U.S. Pat. Nos. 8,518,981, 8,598,218, and 8,598,219, dated Apr. 29, 2014.
Mylan Institutional LLC Paragraph IV Letter regarding U.S. Pat. Nos. 7,947,724, 7,947,725, 7,960,424, 8,518,981, 8,598,218, and 8,598,219, dated May 16, 2014.
Bedford Laboratories division of Ben Venue Laboratories, Inc. Paragraph IV Letter regarding U.S. Pat. No. 8,729,094, dated May 29, 2014.
Defendants' Opening Claim Construction Brief regarding U.S. Pat. No. 8,598,219, dated Jun. 19, 2014 (D.N.J. 11-3962, consolidated).
Answer, Affirmative Defenses and Counterclaims of Defendants Cipla Ltd. and Cipla USA, Inc. regarding U.S. Pat. Nos. 7,947,724, 7,947,725, 7,960,424, 8,518,981, 8,598,218 and 8,598,219 dated Apr. 29, 2014 (D. Del. Case No. 14-427).
Complaint for Patent Infringement filed by Helsinn Healthcare S.A. and Roche Palo Alto LLC against Mylan Inc. and Mylan Institutional LLC regarding U.S. Pat. Nos. 7,947,724, 7,947,725, 7,960,424, 8,598,219, and 8,729,094, dated Jun. 4, 2014 (D. Del. Case No. 14-709).
G. Steele, Preformulation predictions from small amounts of compound as an aid to candidate drug selection, in Pharmaceutical Preformulation and Formulation: A Practical Guide from Candidate Drug Selection to Commercial Dosage Form, Ch. 3, pp. 21-95 (Gibson ed., CRC Press 1st ed. 2001).
G. Steele, Preformulation as an aid to product design in early drug development, in Pharmaceutical Preformulation and Formulation: A

(56) **References Cited**

OTHER PUBLICATIONS

Practical Guide from Candidate Drug Selection to Commercial Dosage Form, Ch. 6, pp. 175-237 (Gibson ed., CRC Press 1st ed. 2001).
M. Gibson, Product optimisation, in Pharmaceutical Preformulation and Formulation: A Practical Guide from Candidate Drug Selection to Commercial Dosage Form, Ch. 8, pp. 295-329 (Gibson ed., CRC Press 1st ed. 2001).
Mylan Institutional LLC Paragraph IV Letter regarding U.S. Pat. No. 8,729,094, dated Jun. 27, 2014.
Ben Venue Laboratories, Inc.'s Opening Claim Construction Brief, dated Apr. 17, 2014 (D. Del. Case No. 13-688, consolidated).
Ben Venue Laboratories, Inc.'s Answering Claim Construction Brief, dated Jul. 8, 2014 (D. Del. Case No. 13-688, consolidated).
Answer, Defenses and Counterclaims of Mylan Institutional LLC regarding U.S. Pat. Nos. 7,947,724, 7,947,725, 7,960,424, 8,598,219, and 8,729,094, dated Jun. 26, 2014 (D. Del. Case No. 14-709).
Aurobindo Pharma Ltd. Paragraph IV Letter regarding U.S. Pat. No. 8,729,094, dated Jul. 25, 2014.
Defendants' Responsive Claim Construction Brief regarding U.S. Pat. No. 8,598,219, dated Jul. 17, 2014 (D.N.J. 11-3962, consolidated).
Cipla Ltd. Paragraph IV Letter regarding U.S. Pat. No. 8,729,094, dated Aug. 6, 2014.
Teva Pharmaceuticals USA, Inc Paragraph IV Letter regarding U.S. Pat. No. 8,729,094, dated Aug. 29, 2014.
Expert Report of Patrick P. DeLuca, Ph.D. with Respect to U.S. Pat. No. 8,598,219, dated Aug. 15, 2014 (D.N.J. 11-3962, consolidated).
Expert Report of David G. Frame, Pharm.D. with Respect to U.S. Pat. No. 8,598,219, dated Aug. 15, 2014 (D.NJ. 11-3962, consolidated).
Opening Expert Report of John P. Fruehauf, M.D., Ph.D. for U.S. Pat. No. 8,598,219, dated Aug. 15, 2014 (D.N.J. 11-3962, consolidated).
Opening Expert Report of Lee Kirsch, Ph.D. for U.S. Pat. No. 8,598,219, dated Aug. 15, 2014 (D.N.J. 11-3962, consolidated).
Expert Report of Maurie Markman, M.D. with Respect to U.S. Pat. No. 8,598,219, dated Aug. 15, 2014 (D.N.J. 11-3962, consolidatd).
Opening Expert Report of Paul Myrdal, Ph.D. for U.S. Pat. No. 8,598,219, dated Aug. 15, 2014 (D.N.J. 11-3962, consolidated).
Second Opening Expert Report of Dr. Bert Spilker with Respect to U.S. Pat. No. 8,598,219, dated Aug. 15, 2014 (D.N.J. 11-3962, consolidated).
K. A. Connors, Introduction to Chemical Kinetics, Chemical Kinetics the Study of Reaction Rates in Solution, John Wiley & Sons, Inc., 1990, Ch. 1, pp. 1-15.
R. G. Strickley, Parenteral formulations of small molecule therapeutics marketed in the United States (1999)—Part I. *PDA J. Pharm. Sci. Technol*. 53:324-349 (1999).
Physicians' Desk Reference, entries for Hespan® (pp. 933-935) and Hyperstat® I.V. Diazoxide Injection (pp. 2848-2849) (53rd ed. 1999).
Physicians' Desk Reference for Astromorph/PF® (pp. 594-595); Baxter's Atrophine Sulfate Injection (p. 858); Baxter's Dobutamine Hydrochloride Injection (p. 861); Duramorph® (p. 863); Baxter's Fentanyl Citrate Injection (p. 868); Baxter's Metoclopramide Injection (p. 871); Baxter's Phenylephrine Hydrochloride Injection (pp. 872-873); Robinul® (p. 873; 2940-42); Phenytoin Sodium Injection (p. 1312); and Diflucan® (pp. 2681-2685) (56th ed. 2002).
The United States Pharmacopeia (USP 26) The National Formulary (NF 21), Official from Jan. 1, 2003, entries for Atrophine Sulfate Injection (p. 192); Diazoxide Injection (p. 591); Dobutamine Hydrochloride Injection (p. 652); Fentanyl Citrate Injection (p. 781); Glycopyrrolate Injection (p. 870); Lidocaine Hydrochloride and Dextrose Injection (pp. 1079-1080); Metoclopramide Injection (pp. 1217-1218); Morphine Sulfate Injection (pp. 1254-1255); Phenylephrine Hydrochloride Injection (pp. 1459-1460); Phenytoin Sodium Injection (pp. 1471-1472); Potassium Chloride for Injection (pp. 1503-1504) (2002).
HELSN0004208 (2002).
Full Prescribing Information for Aloxi (palonosetron HCI) Injection for Intravenous Use (2014).
Preformulation Book, Syntex Research, pp. C1-C7, C1-C19, and C1-C26 (1993).
Accord Healthcare, Inc.'s Petition for Post Grant Review of U.S. Pat. No. 8,598,219 dated Sep. 2, 2014.
Exhibit 1015 to Accord Healthcare, Inc.'s Petition for Post Grant Review of U.S. Pat. No. 8,598,219, Declaration of Arnold J. Repta, Ph.D. dated Sep. 2, 2014.
Rebuttal Expert Report of Gordon L. Amidon, Ph.D. concerning U.S. Pat. No. 8,598,219, dated Sep. 15, 2014 (D.N.J. 11-3962, consolidated).
Rebuttal Expert Report of Keith A. Candiotti, M.D. with respect to U.S. Pat. No. 8,598,219, dated Sep. 15, 2014 (D.N.J. 11-3962, consolidated).
Second Rebuttal Expert Report of Carl C. Peck, M.D. dated Sep. 15, 2014 (D.N.J. 11-3962, consolidated).
Rebuttal Expert Report of Tanios Bekaii-Saab, M.D. with respect to U.S. Pat. No. 8,598,219, dated Sep. 15, 2014 (D.N.J. 11-3962, consolidated).
Answer and Counterclaims of Dr. Reddy's Laboratories, Ltd. and Dr. Reddy's Laboratories, Inc. to Complaint for Patent Infringement regarding U.S. Pat. No. 8,729,094 dated Sep. 5, 2014 (D.N.J. Case No. 14-4274).
Dr. Reddy's Laboratories, Ltd.'s and Dr. Reddy's Laboratories, Inc.'s Paragraph IV Letter regarding U.S. Pat. Nos. 8,518,981, No. 8,598,218, 8,598,219, and 8,729,094, dated Sep. 19, 2014.
Dr. Reddy's Laboratories, Ltd.'s and Dr. Reddy's Laboratories, Inc.'s Paragraph IV Letter regarding U.S. Pat. Nos. 8,518,981, 8,598,218, 8,598,219, and 8,729,094, dated Sep. 24, 2014.
R. M. Eglen and D. W. Bonhaus, "5-Hydroxytryptamine (5-HT)$_3$ Receptors: Molecular Biology, Pharmacology and Therapeutic Importance," Curr Pharm Des. 2:367-74 (1996).
"Helsinn Announces That Patient Enrollment for Phase III Palonosetron Trials Progresses Both in USA and Europe," PR Newswire, Sep. 14, 2000.
G. Piraccini, et al., "A Novel Anti-Emetic Agent, Palonosetron (RS 25259-197): Evidence From Phase I Trials," Support Care Cancer, Jun. 2001, vol. 9, No. 4, Abstract No. P-41 and associated poster presentation.
RS-25259-197, Drugs Fut. 1996, 21(9):906-910 (1996).
Palonosetron Hydrochloride RS-25259-197, Drugs Fut. 2000, 25(9):982 (Sep. 2000).
Palonosetron Hydrochloride, Drugs Fut. 2001, 26(9):911 (Sep. 2001).
R. E. Leak and J. D. Woodford, "Pharmaceutical Development of Ondansetron Injection," Eur J Cancer Clin Oncol. 25(Suppl 1):S67-69 (1989).
Reply Expert Report of David G. Frame, Pharm. D. with respect to U.S. Pat. No. 8,598,219 dated Oct. 10, 2014 (D.N J. 11-3962, consolidated).
Reply Expert Report of Maurie Markman, M.D. with respect to U.S. Pat. No. 8,598,219 dated Oct. 10, 2014 (D.N.J. 11-3962, consolidated).
Reply Expert Report of John P. Fruehauf, M.D., Ph.D. for U.S. Pat. No. 8,598,219 dated Oct. 10, 2014 (D.N.J. 11-3962, consolidated).
Reply Expert Report of Lee Kirsch, Ph.D. for U.S. Pat. No. 8,598,219 dated Oct. 10, 2014 (D.N.J. 11-3962, consolidated).
Reply Expert Report of Paul Myrdal, Ph.D. for U.S. Pat. No. 8,598,219 dated Oct. 10, 2014 (D.N.J. 11-3962, consolidated).
Second Reply Expert Report of Dr. Bert Spilker regarding U.S. Pat. No. 8,598,219 dated Oct. 10, 2014 (D.N.J. 11-3962, consolidated).
Exela Pharma Sciences LLC's Paragraph IV Letter regarding U.S. Pat. Nos. 7,947,724, 7,947,725, 7,960,424, 8,518,981, 8,598,218, 8,598,219, and 8,729,094, dated Oct. 16, 2014.
Final Joint Claim Construction Chart regarding U.S. Pat. Nos. 7,947,724, 7,947,725, 7,960,424, 8,598,219, and 8,729,094 dated Oct. 24, 2014 (D. Del. Case Nos. 13-688 and 14-709).
Mylan Institutional LLC's Opening Claim Construction Brief dated Dec. 5, 2014 (D. Del. Case No. 13-688, consolidated).
Defendants Cipla Ltd. and Cipla USA, Inc.'s Corrected Opening Claim Construction Brief dated Jan. 27, 2015 (D. Del. Case No. 13-688, consolidated).
Plaintiffs' Opening Claim Construction Brief dated Dec. 5, 2014 (D. Del. Case No. 13-688, consolidated).

(56) **References Cited**

OTHER PUBLICATIONS

Defendants Teva Pharmaceuticals USA, Inc. and Teva Pharmaceutical Industries Ltd. Corrected Answer to Complaint for Patent Infringement and Counterclaim for Declaratory Judgment regarding U.S. Pat. No. 8,729,094 dated Jan. 8, 2015 (D.N.J. Case No. 14-6341).
Termination of the Proceeding (Case No. PGR2014-00010) dated Nov. 24, 2014.
Declaration of Dr. Neervalur Raghavan, Ph.D. with Exhibits 1-25, dated Sep. 28, 2014.
Gavis Pharma LLC's Paragraph IV Letter regarding U.S. Pat. Nos. 7,947,724, 7,947,725, 7,960,424, 8,518,981, 8,598,218, 8,598,219, and 8,729,094, dated Dec. 31, 2014.
Answer, Defenses, and Counterclaims of Defendants Exela Pharma Sciences, LLC, Exela Pharmsci, Inc. and Exela Holdings, Inc. to Complaint regarding U.S. Pat. Nos. 8,518,981 and 8,598,218 redacted version dated Dec. 29, 2014 (D. Del. Case No. 14-1444).
Defendant Mylan Institutional, LLC's Responsive Claim Construction Brief dated Jan. 14, 2015 (D. Del. Case No. 13-688, consolidated).
Defendants Cipla Ltd. and Cipla USA, Inc.'s Corrected Answering Claim Construction Brief dated Jan. 27, 2015 (D. Del. Case No. 13-688, consolidated).
Plaintiffs' Responsive Claim Construction Brief, redacted public version dated Jan. 20, 2015 (D. Del. Case No. 13-688, consolidated).
On Sale and Public Use Bars to Patentability After AIA: Minimizing the Risk of Patent Ineligibility or Invalidation, Cover and Slide 74, Nov. 7, 2013.
Hospira Inc.'s Paragraph IV Letter regarding U.S. Pat. Nos. 7,947,724, 7,947,725, 7,960,424, 8,518,981, 8,598,218, 8,598,219, and 8,729,094, dated Feb. 10, 2015.
Par Pharmaceutical, Inc.'s Paragraph IV Letter regarding U.S. Pat. Nos. 7,947,724, 7,947,725, 7,960,424, 8,518,981, 8,598,218, 8,598,219, and 8,729,094, dated Feb. 10, 2015.
Feb. 9, 2009 Bonadeo Declaration.
Perez, et al., Comparable safety and antiemetic efficacy of a brief (30-second bolus) intravenous granisetron infusion and a standard (15-minute) intravenous ondansetron infusion in breast cancer patients receiving moderately emetogenic chemotherapy. Cancer J. Sci. Am. vol. 4, No. 1, pp. 52-58, 1998.
Bedford Laboratories division of Ben Venue Laboratories, Inc. Paragraph IV Letter regarding U.S. Pat. Nos. 7,947,724, 7,947,725, and 7,960,424, dated Aug. 13, 2013.
Aurobindo Pharma Ltd. Paragraph IV notice regarding U.S. Pat. No. 8,518,981, dated Sep. 19, 2013.
Dr. Reddy's Laboratories, Ltd.'s and Dr. Reddy's Laboratories, Inc.'s Amended Invalidity Contentions Pursuant to L. Pat. R. 3.6(c), dated Jul. 8, 2013 (D.N.J. Case Nos. 11-3962 and 11-5579; consolidated).
Sandoz Inc.'s Second Amended Invalidity Contentions Pursuant to L. Pat. R. 3.7, dated Jul. 5, 2013 (D.N.J. Case Nos. 11-3962 and 11-5579; consolidated).
Defendants Teva Pharmaceuticals USA, Inc. and Teva Pharmaceutical Industries, Ltd.'s First Amended Invalidity Contentions Pursuant to L. Pat. R. 3.6(c), dated Jul. 5, 2013 (D.N.J. Case Nos. 11-3962 and 11-5579; consolidated).
Opening Expert Report of Dr. Bert Spilker, dated Sep. 9, 2013 (D.N.J. Case Nos. 11-3962 and 11-5579; consolidated).
Expert Report of David G. Frame, Pharm. D., dated Sep. 5, 2013 (D.N.J. Case Nos. 11-3962 and 11-5579; consolidated).
Expert Report of Lee Kirsch, Ph.D., dated Sep. 9, 2013 (D.N.J. Case Nos. 11-3962 and 11-5579; consolidated).
Expert Report of Patrick P. DeLuca, Ph.D., dated Sep. 9, 2013 (D.N.J. Case Nos. 11-3962 and 11-5579; consolidated).
Expert Report of Paul Myrdal, Ph.D., dated Sep. 9, 2013 (D.N.J. Case Nos. 11-3962 and 11-5579; consolidated).
Complaint for patent infringement filed by Helsinn Healthcare S.A. and Roche Palo Alto LLC against Ben Venue Laboratories, Inc. d/b/a Bedford Laboratories regarding U.S. Pat. Nos. 7,947,724, 7,947,725, 7,960,424, and 8,518,981 dated Sep. 25, 2013 (D. Del. Case No. 13-1612).
Reply Expert Report of Patrick P. DeLuca, Ph.D., dated Nov. 22, 2013 (D.N.J. Case Nos. 11-3962 and 11-5579; consolidated).
Reply Expert Report of David G. Frame, Pharm. D., dated Nov. 27, 2013 (D.N.J. Case Nos. 11-3962 and 11-5579; consolidated).
Reply Expert Report of Jack Geltosky, Ph.D., dated Nov. 22, 2013 (D.N.J. Case Nos. 11-3962 and 11-5579; consolidated).
Reply Expert Report of Lee Kirsch, Ph.D., dated Nov. 22, 2013 (D.N.J. Case No. 11-3962 and 11-5579; consolidated).
Reply Expert Report of Paul Myrdal, Ph.D., dated Nov. 22, 2013 (D.N.J. Case No. 11-3962 and 11-5579; consolidated).
Reply Expert Report of Dr. Bert Spilker, dated Nov. 22, 2013 (D.N.J. Case No. 11-3962 and 11-5579; consolidated).
Accord Healthcare, Inc. Paragraph IV Letter regarding U.S. Pat. No. 8,518,981 dated Oct. 2, 2013.
Bedford Laboratories division of Ben Venue Laboratories, Inc. Paragraph IV Letter regarding U.S. Pat. No. 8,518,981 dated Oct. 16, 2013.
Sandoz Inc. Paragraph IV Letter regarding U.S. Pat. No. 8,518,981 dated Dec. 16, 2013.
Aurobindo Pharma Ltd. Paragraph IV Letter regarding U.S. Pat. Nos. 8,598,218 and 8,598,219 dated Jan. 21, 2014.
Sandoz Inc. Paragraph IV Letter regarding U.S. Pat. Nos. 8,598,218 and 8,598,219 dated Feb. 3, 2014.
Bedford Laboratories division of Ben Venue Laboratories, Inc. Paragraph IV Letter regarding U.S. Pat. Nos. 8,598,218 and 8,598,219 dated Feb. 6, 2014.
Defendants Aurobindo Pharma Ltd.'s and Auromedics Pharma LLC's Amended Answer, Affirmative Defenses, and Counterclaims regarding U.S. Pat. Nos. 7,947,724, 7,947,725, 7,960,424, 8,518,981, 8,598,218, and 8,598,219, dated Feb. 11, 2014 (D. Del. Case No. 13-688).
Ben Venue Laboratories, Inc.'s Answer and Counterclaims to Amended Complaint regarding U.S. Pat. Nos. 7,947,724, 7,947,725, 7,960,424, 8,518,981, 8,598,218, and 8,598,219, dated Feb. 24, 2014 (D. Del. Case No. 13-1612).
Complaint for Patent Infringement filed by Helsinn Healthcare S.A. and Roche Palo Alto LLC against Accord Healthcare, Inc. and Intas Pharmaceuticals Ltd regarding U.S. Pat. Nos. 8,598,218 and 8,598,219 dated Dec. 27, 2013 (D. Del. Case No. 13-2101).
Cipla Limited Paragraph IV Letter regarding U.S. Pat. Nos. 7,947,724, 7,947,725, 7,960,424, 8,518,981, 8,598,218, and 8,598,219 dated Feb. 24, 2014.
Dr. Reddy's Laboratories, Ltd.'s and Dr. Reddy's Laboratories, Inc.'s Invalidity Contentions regarding U.S. Pat. Nos. 8,518,981, 8,598,218, and 8,598,219 dated Mar. 17, 2014 (D.N.J. Case No. 13-5815) .
Sandoz Inc.'s Invalidity Contentions Pursuant to L. Pat. R. 3.3 and 3.6(c) regarding U.S. Pat. Nos. 8,518,981, 8,598,218, and 8,598,219 dated Mar. 17, 2014 (D.N.J. Case No. 13-5815).
Teva Pharmaceuticals USA, Inc. and Teva Pharmaceutical Industries Ltd.'s Invalidity Contentions Pursuant to L. Pat. R. 3.6(c) regarding U.S. Pat. Nos. 8,518,981, 8,598,218, and 8,598,219 dated Mar. 17, 2014 (D.N.J. Case No. 13-5815).

* cited by examiner

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_3 (5-hydroxytryptamine) receptor antagonists has been developed that treat such emesis by antagonizing cerebral functions associated with the 5-HT_3 receptor. See *Drugs Acting on 5-Hydroxytryptamine Receptors*: The Lancet Sep. 23, 1989 and references cited therein. Drugs within this class include ondansetron, granisetron, alosetron, tropisetron, and dolasetron. These 5-HT_3 antagonists are often administered intravenously shortly before chemotherapy or radiotherapy is initiated, and can be administered more than once during a cycle of chemotherapy or radiotherapy. In addition, they are often supplied as tablets or oral elixirs to either supplement an intravenous administration, or to ease home usage of the drug if the patient is self-administering the chemotherapeutic regimen.

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

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

Ingredient	Mg
Palonosetron 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 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® (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_3 receptor antagonist and its pharmaceutically acceptable carriers that would facilitate making a formulation with this increased stability.

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

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

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

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

SUMMARY OF THE INVENTION

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

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

In one aspect, the inventors have discovered that formulations which include the active ingredient palonosetron require in some instances only $\frac{1}{10}^{th}$ 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.

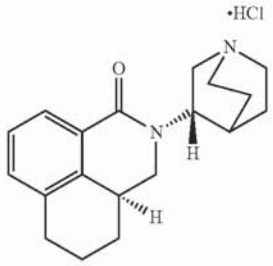
DETAILED DESCRIPTION OF THE INVENTION

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:



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, camphorsulfonicacid, 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 $\frac{1}{10}^{th}$ 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 comprise 5 ml. of solution, which equates to about 0.25 mg of palonosetron at a concentration of about 0.05 mg/ml.

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

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

- The formulation may comprise palonosetron or a pharmaceutically acceptable salt thereof in a concentration from about 0.02 mg/mL to about 1.0 mg/mL, from about 0.03 mg/mL to about 0.2 mg/mL palonosetron hydrochloride, and most optimally about 0.05 mg/ml.
- The formulation may comprise citrate buffer in a concentration of from about 10 to about 40 millimoles, or 15-30 millimoles.
- The formulation may comprise EDTA in a concentration of from about 0.005 mg/ml to about 1.0 mg/ml, or about 0.3 to about 0.7 mg/ml, and most optimally about 0.5 mg/ml.

The inventors have further discovered that the addition of mannitol and a chelating agent can increase the stability of palonosetron formulations. Therefore, in still another embodiment the invention provides a pharmaceutically stable solution for preventing or reducing emesis comprising a) palonosetron or a pharmaceutically acceptable salt thereof and b) a pharmaceutically acceptable carrier, wherein the pharmaceutically acceptable carrier comprises a chelating agent and mannitol. Similarly, in another embodiment the invention provides a method of formulating a pharmaceutically stable solution of palonosetron comprising admixing a) palonosetron or a pharmaceutically acceptable salt thereof and b) a pharmaceutically acceptable carrier, wherein the pharmaceutically acceptable carrier comprises a chelating agent and mannitol. The chelating agent is preferably EDTA, and, in various embodiments the chelating agent is present in a concentration of from about 0.005 to about 1.0 mg/mL or from about 0.05 mg/mL to about 1.0 mg/mL or from about 0.3 to about 0.7 mg/ml, or most optimally about 0.5 mg/mL. In various embodiments the mannitol is present in a concentration of from about 10.0 mg/ml to about 80.0 mg/ml, from about 20.0 mg/mL to about 60.0 mg/ml, or from about 40.0 to about 45.0 mg/ml.

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

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

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

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

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

EXAMPLES

Example 1

Stabilizing pH

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

Example 2

Stabilizing Concentration Ranges

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

Example 3

Tonicifying Agent

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

Example 4

Formulation I

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

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

*calculated as a free base

Example 5

Formulation II

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

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

*calculated as a free base

Example 6

Stability of Palonosetron without Dexamethasone

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

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

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

Example 7

Stability of Palonosetron with Dexamethasone

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

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

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

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

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[a]
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[b] plus rubber stopper[c]

[a]Calculated based on the weight of free base.
[b]Polyethylene multilayer film infusion bag.
[c]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 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

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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