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**UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY**

HEL SINN HEALTHCARE S.A. and
ROCHE PALO ALTO LLC,

Plaintiffs,

v.

DR. REDDY'S LABORATORIES, LTD.,
DR. REDDY'S LABORATORIES, INC.,
SANDOZ INC., TEVA PHARMACEUTICALS
USA, INC., and TEVA PHARMACEUTICAL
INDUSTRIES, LTD.,

Defendants.

Civil Action No. _____

**COMPLAINT FOR
PATENT INFRINGEMENT**

(Filed Electronically)

Dr. Reddy's Laboratories, Ltd., et al.

v.

Helsinn Healthcare S.A., et al.

U.S. Patent No. 9,111,111 G

Reddy Exhibit 1005

Plaintiffs Helsinn Healthcare S.A. (“Helsinn”) and Roche Palo Alto LLC (“Roche”), for its Complaint against Defendants Dr. Reddy’s Laboratories Ltd. (“Reddy Ltd.”), Dr. Reddy’s Laboratories Inc. (“Reddy Inc.”), Sandoz Inc. (“Sandoz”), Teva Pharmaceuticals USA, Inc. (“Teva USA”), and Teva Pharmaceutical Industries Ltd. (“Teva Ltd.”), hereby allege as follows:

THE PARTIES

1. Plaintiff Helsinn is a Swiss corporation having its principal place of business at Via Pian Scairolo, 9, CH-6912 Lugano-Pazzallo, Switzerland.
2. Plaintiff 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, Defendant Reddy Ltd. is an Indian corporation having a place of business at 8-2-337, Road No. 3, Banjara Hills, Hyderabad - 500034, Andhra Pradesh, India. Upon information and belief, Reddy Ltd., itself and through its wholly owned subsidiary and agent Defendant Reddy Inc. (referred to collectively as “Reddy”), manufactures generic drugs for sale and use throughout the United States, including in this judicial district. Upon information and belief, Reddy Ltd. has appointed Lee Banks, Esq. of Reddy Inc., 200 Somerset Corporate Boulevard, Floor 7, Bridgewater, New Jersey 08807, as its agent in New Jersey authorized to accept service of process in this action. Reddy Ltd. has previously consented to personal jurisdiction in this Court.
4. Upon information and belief, Defendant Reddy Inc. is a corporation organized and existing under the laws of the State of New Jersey, having a place of business at 200 Somerset Corporate Boulevard, Floor 7, Bridgewater, New Jersey 08807, and is a wholly owned subsidiary and agent of Defendant Reddy Ltd. Upon information and belief, Reddy Inc.

is registered to do business in New Jersey and does business in this judicial district. Upon information and belief, Reddy Inc. has appointed Lee Banks, Esq. of Reddy Inc., 200 Somerset Corporate Boulevard, Floor 7, Bridgewater, New Jersey 08807, as its agent in New Jersey authorized to accept service of process in this action. Reddy Inc. has previously consented to personal jurisdiction in this Court.

5. Upon information and belief, Defendant Sandoz is a corporation organized and existing under the laws of the State of Colorado, having a place of business at 506 Carnegie Center, Suite 400, Princeton, New Jersey 08540. Upon information and belief, Sandoz is registered to do business in New Jersey and does business in this judicial district. Upon information and belief, Sandoz has appointed Stephen R. Auten, Esq. of Sandoz, 506 Carnegie Center, Suite 400, Princeton, New Jersey 08540, as its agent in New Jersey authorized to accept service of process in this action. Sandoz has previously consented to personal jurisdiction in this Court.

6. Upon information and belief, Defendant Teva USA is a corporation organized and existing under the laws of the State of Delaware, having a place of business at 400 Chestnut Ridge Road, Woodcliff Lake, New Jersey 07677. Teva USA is a wholly owned subsidiary and agent of Defendant Teva Ltd. (referred to collectively as “Teva”). Upon information and belief, Teva USA has facilities in New Jersey, is registered to do business in New Jersey, and does business in this judicial district. Teva USA has previously consented to personal jurisdiction in this Court.

7. Upon information and belief, Defendant Teva Ltd. is an Israeli corporation having a place of business at 5 Basel Street, Petah Tikva 49131, Israel. Upon information and belief, Teva Ltd., itself and through its wholly owned subsidiary and agent Defendant Teva USA,

manufactures generic drugs for sale and use throughout the United States, including in this judicial district. Teva Ltd. has previously consented to personal jurisdiction in this Court.

NATURE OF THE ACTION

8. This is a civil action concerning the infringement of United States Patent No. 7,947,724 (“the ’724 patent”) and United States Patent No. 7,947,725 (“the ’725 patent”). This action arises under the patent laws of the United States, 35 U.S.C. §§ 100 *et seq.*, and the Declaratory Judgment Act, 28 U.S.C. §§ 2201-02.

JURISDICTION AND VENUE

9. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a).

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

11. This Court has personal jurisdiction over each of the Defendants by virtue of the fact that, *inter alia*, each Defendant has committed, aided, abetted, contributed to, and/or participated in the commission of a tortious act of patent infringement that has led to foreseeable harm and injury to Plaintiffs. This Court has personal jurisdiction over each of the Defendants for the additional reasons set forth above and below, and for other reasons that will be presented to the Court if such jurisdiction is challenged.

12. This Court has personal jurisdiction over Defendant Reddy Ltd.

13. This Court has personal jurisdiction over Defendant Reddy Inc.

14. This Court has personal jurisdiction over Defendant Sandoz.

15. This Court has personal jurisdiction over Defendant Teva USA.

16. This Court has personal jurisdiction over Defendant Teva Ltd.

THE PATENTS

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

18. On May 24, 2011, the '725 patent, titled "Liquid Pharmaceutical Formulations of Palonosetron," was duly and legally issued to Helsinn and Roche as assignees. A copy of the '725 patent is attached as Exhibit B.

ACTS GIVING RISE TO THIS ACTION

COUNT I – INFRINGEMENT OF THE '724 PATENT BY REDDY

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

20. Upon information and belief, Defendant Reddy submitted ANDA No. 201533 to the United States Food and Drug Administration ("FDA") under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA No. 201533 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 the '724 patent. ANDA No. 201533 specifically seeks FDA approval to market generic versions 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.

21. ANDA No. 201533 alleges under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '724 patent are invalid.

22. Reddy's submission to the FDA of ANDA No. 201533, including the § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '724 patent under 35 U.S.C. § 271(e)(2)(A).

23. Reddy Ltd. and Reddy Inc. are jointly and severally liable for any infringement of the '724 patent. This is because, upon information and belief, Reddy Ltd. and Reddy Inc. actively and knowingly caused to be submitted, assisted with, participated in, contributed to, and/or directed the submission of the ANDA No. 201533 and the § 505(j)(2)(A)(vii)(IV) allegations to the FDA.

24. Reddy's active and knowing participation in, contribution to, aiding, abetting, and/or inducement of the submission to the FDA of ANDA No. 201533 and the § 505(j)(2)(A)(vii)(IV) allegations constitutes infringement of the '724 patent under 35 U.S.C. § 271(e)(2)(A).

25. Plaintiffs are entitled to a declaration that, if Reddy commercially manufactures, uses, offers for sale, 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, Reddy would infringe the '724 patent under 35 U.S.C. § 271(a), (b), and/or (c).

26. Plaintiffs will be irreparably harmed by Reddy'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 '724 PATENT BY SANDOZ

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

28. Upon information and belief, Defendant Sandoz submitted ANDA No. 202521 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA No. 202521 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

the '724 patent. ANDA No. 202521 specifically seeks FDA approval to market generic versions 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.

29. ANDA No. 202521 alleges under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '724 patent are invalid.

30. Sandoz's submission to the FDA of ANDA No. 202521, including the § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '724 patent under 35 U.S.C. § 271(e)(2)(A).

31. Plaintiffs are entitled to a declaration that, if Sandoz commercially manufactures, uses, offers for sale, 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, Sandoz would infringe the '724 patent under 35 U.S.C. § 271(a), (b), and/or (c).

32. Plaintiffs will be irreparably harmed by Sandoz'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 '724 PATENT BY TEVA

33. Plaintiffs reallege paragraphs 1-32 as if fully set forth herein.

34. Upon information and belief, Defendant Teva submitted ANDA No. 090713 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA No. 090713 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 the '724 patent. ANDA No. 090713 specifically seeks FDA approval to market generic versions

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.

35. ANDA No. 090713 alleges under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '724 patent are invalid.

36. Teva's submission to the FDA of ANDA No. 090713, including the § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '724 patent under 35 U.S.C. § 271(e)(2)(A).

37. Teva Ltd. and Teva Inc. are jointly and severally liable for any infringement of the '724 patent. This is because, upon information and belief, Teva Ltd. and Teva Inc. actively and knowingly caused to be submitted, assisted with, participated in, contributed to, and/or directed the submission of the ANDA No. 090713 and the § 505(j)(2)(A)(vii)(IV) allegations to the FDA.

38. Teva's active and knowing participation in, contribution to, aiding, abetting, and/or inducement of the submission to the FDA of ANDA No. 090713 and the § 505(j)(2)(A)(vii)(IV) allegations constitutes infringement of the '724 patent under 35 U.S.C. § 271(e)(2)(A).

39. Plaintiffs are entitled to a declaration that, if Teva commercially manufactures, uses, offers for sale, 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, Teva would infringe the '724 patent under 35 U.S.C. § 271(a), (b), and/or (c).

40. Plaintiffs will be irreparably harmed by Teva'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 '725 PATENT BY REDDY

41. Plaintiffs reallege paragraphs 1-40 as if fully set forth herein.

42. Upon information and belief, Defendant Reddy submitted ANDA No. 201533 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA No. 201533 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 the '725 patent. ANDA No. 201533 specifically seeks FDA approval to market generic versions 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 '725 patent.

43. ANDA No. 201533 alleges under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '725 patent are invalid.

44. Reddy's submission to the FDA of ANDA No. 201533, including the § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '725 patent under 35 U.S.C. § 271(e)(2)(A).

45. Reddy Ltd. and Reddy Inc. are jointly and severally liable for any infringement of the '725 patent. This is because, upon information and belief, Reddy Ltd. and Reddy Inc. actively and knowingly caused to be submitted, assisted with, participated in, contributed to, and/or directed the submission of the ANDA No. 201533 and the § 505(j)(2)(A)(vii)(IV) allegations to the FDA.

46. Reddy's active and knowing participation in, contribution to, aiding, abetting, and/or inducement of the submission to the FDA of ANDA No. 201533 and the § 505(j)(2)(A)(vii)(IV) allegations constitutes infringement of the '725 patent under 35 U.S.C. § 271(e)(2)(A).

47. Plaintiffs are entitled to a declaration that, if Reddy commercially manufactures, uses, offers for sale, 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, Reddy would infringe the '725 patent under 35 U.S.C. § 271(a), (b), and/or (c).

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

COUNT V – INFRINGEMENT OF THE '725 PATENT BY SANDOZ

49. Plaintiffs reallege paragraphs 1-48 as if fully set forth herein.

50. Upon information and belief, Defendant Sandoz submitted ANDA No. 202521 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA No. 202521 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 the '725 patent. ANDA No. 202521 specifically seeks FDA approval to market generic versions 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 '725 patent.

51. ANDA No. 202521 alleges under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '725 patent are invalid.

52. Sandoz's submission to the FDA of ANDA No. 202521, including the § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '725 patent under 35 U.S.C. § 271(e)(2)(A).

53. Plaintiffs are entitled to a declaration that, if Sandoz commercially manufactures, uses, offers for sale, 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, Sandoz would infringe the '725 patent under 35 U.S.C. § 271(a), (b), and/or (c).

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

COUNT VI – INFRINGEMENT OF THE '725 PATENT BY TEVA

55. Plaintiffs reallege paragraphs 1-54 as if fully set forth herein.

56. Upon information and belief, Defendant Teva submitted ANDA No. 090713 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA No. 090713 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 the '725 patent. ANDA No. 090713 specifically seeks FDA approval to market generic versions 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 '725 patent.

57. ANDA No. 090713 alleges under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '725 patent are invalid.

58. Teva's submission to the FDA of ANDA No. 090713, including the § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '725 patent under 35 U.S.C. § 271(e)(2)(A).

59. Teva Ltd. and Teva Inc. are jointly and severally liable for any infringement of the '725 patent. This is because, upon information and belief, Teva Ltd. and Teva Inc. actively and knowingly caused to be submitted, assisted with, participated in, contributed to, and/or directed the submission of the ANDA No. 090713 and the § 505(j)(2)(A)(vii)(IV) allegations to the FDA.

60. Teva's active and knowing participation in, contribution to, aiding, abetting, and/or inducement of the submission to the FDA of ANDA No. 090713 and the § 505(j)(2)(A)(vii)(IV) allegations constitutes infringement of the '725 patent under 35 U.S.C. § 271(e)(2)(A).

61. Plaintiffs are entitled to a declaration that, if Teva commercially manufactures, uses, offers for sale, 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, Teva would infringe the '725 patent under 35 U.S.C. § 271(a), (b), and/or (c).

62. Plaintiffs will be irreparably harmed by Teva'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 Defendants Reddy Ltd., Reddy Inc., Sandoz, Teva USA, and Teva Ltd. have infringed the '724 and '725 patents by submitting the aforesaid ANDAs;

B. An Order be issued pursuant to 35 U.S.C. § 271(e)(4)(A) that the effective date of any approval of any of Defendants' ANDAs identified in this Complaint be a date that is

not earlier than the expiration dates of the '724 patent and '725 patent, or any later expiration of exclusivity for the '724 patent or '725 patent to which Plaintiffs are or become entitled;

C. An Order be issued that Defendants Reddy Ltd., Reddy Inc., Sandoz, Teva USA, and Teva Ltd., their officers, agents, servants and employees, and those persons in active concert or participation with any of them, are preliminarily and permanently enjoined from commercially manufacturing, using, offering for sale, importing, or selling 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 or '725 patents, prior to the expiration of the '724 or '725 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: July 8, 2011

Respectfully submitted,

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Roche Palo Alto LLC*

*Attorneys for Plaintiffs
Helsinn Healthcare S.A. and
Roche Palo Alto LLC*

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 above-captioned action is not the subject of any other action pending in any court, or of any pending arbitration or administrative proceeding.

Dated: July 8, 2011

Respectfully submitted,

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**UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY**

HEL SINN HEALTHCARE S.A. and
ROCHE PALO ALTO LLC,

Plaintiffs,

v.

DR. REDDY'S LABORATORIES, LTD.,
DR. REDDY'S LABORATORIES, INC.,
SANDOZ INC., TEVA PHARMACEUTICALS
USA, INC., and TEVA PHARMACEUTICAL
INDUSTRIES, LTD.,

Defendants.

Civil Action No. _____

**COMPLAINT FOR
PATENT INFRINGEMENT**

(Filed Electronically)

Plaintiffs Helsinn Healthcare S.A. (“Helsinn”) and Roche Palo Alto LLC (“Roche”), for their Complaint against Defendants Dr. Reddy’s Laboratories, Ltd. (“Reddy Ltd.”), Dr. Reddy’s Laboratories, Inc. (“Reddy Inc.”), Sandoz Inc. (“Sandoz”), Teva Pharmaceuticals USA, Inc. (“Teva USA”), and Teva Pharmaceutical Industries, Ltd. (“Teva Ltd.”), hereby allege as follows:

THE PARTIES

1. Plaintiff Helsinn is a Swiss corporation having a principal place of business at Via Pian Scaiolo, 9, CH-6912 Lugano-Pazzallo, Switzerland.
2. Plaintiff 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, Defendant Reddy Ltd. is an Indian corporation having a principal place of business at 7-1-27, Ameerpet, Hyderabad, Andhra Pradesh, India. Upon information and belief, Reddy Ltd., itself and through its wholly owned subsidiary and agent Defendant Reddy Inc. (referred to collectively as “Reddy”), manufactures generic drugs for sale and use throughout the United States, including in this judicial district. Upon information and belief, Reddy Ltd. has appointed Lee Banks, Esq. of Reddy Inc., 200 Somerset Corporate Boulevard, Floor 7, Bridgewater, New Jersey 08807, as its agent in New Jersey authorized to accept service of process in this action. Reddy Ltd. has previously consented to personal jurisdiction in this Court, including in the related action, *Helsinn Healthcare S.A., et al. v. Dr. Reddy’s Laboratories, Ltd., et al.*, Civil Action No. 11-3962 (MLC)(DEA).
4. Upon information and belief, Defendant Reddy Inc. is a corporation organized and existing under the laws of the State of New Jersey, having a principal place of

business at 200 Somerset Corporate Boulevard, Floor 7, Bridgewater, New Jersey 08807, and is a wholly owned subsidiary and agent of Defendant Reddy Ltd. Upon information and belief, Reddy Inc. is registered to do business in New Jersey and does business in this judicial district. Upon information and belief, Reddy Inc. has appointed Lee Banks, Esq. of Reddy Inc., 200 Somerset Corporate Boulevard, Floor 7, Bridgewater, New Jersey 08807, as its agent in New Jersey authorized to accept service of process in this action. Reddy Inc. has previously consented to personal jurisdiction in this Court, including in the related action, *Helsinn Healthcare S.A., et al. v. Dr. Reddy's Laboratories, Ltd., et al.*, Civil Action No. 11-3962 (MLC)(DEA).

5. Upon information and belief, Defendant Sandoz is a corporation organized and existing under the laws of the State of Colorado, having a principal place of business at 506 Carnegie Center, Suite 400, Princeton, New Jersey 08540. Upon information and belief, Sandoz is registered to do business in New Jersey and does business in this judicial district. Upon information and belief, Sandoz has appointed Alexandra Haner, Esq. of Sandoz, 506 Carnegie Center, Suite 400, Princeton, New Jersey 08540, as its agent in New Jersey authorized to accept service of process in this action. Sandoz has previously consented to personal jurisdiction in this Court, including in the related action, *Helsinn Healthcare S.A., et al. v. Dr. Reddy's Laboratories, Ltd., et al.*, Civil Action No. 11-3962 (MLC)(DEA).

6. Upon information and belief, Defendant Teva USA is a corporation organized and existing under the laws of the State of Delaware, having a place of business at 400 Chestnut Ridge Road, Woodcliff Lake, New Jersey 07677. Teva USA is a wholly owned subsidiary and agent of Defendant Teva Ltd. (referred to collectively as "Teva"). Upon information and belief, Teva USA has facilities in New Jersey, is registered to do business in

New Jersey, and does business in this judicial district. Teva USA has previously consented to personal jurisdiction in this Court, including in the related action *Helsinn Healthcare S.A., et al. v. Dr. Reddy's Laboratories, Ltd., et al.*, Civil Action No. 11-3962 (MLC)(DEA).

7. Upon information and belief, Defendant Teva Ltd. is an Israeli corporation having a place of business at 5 Basel Street, Petah Tikva 49131, Israel. Upon information and belief, Teva Ltd., itself and through its wholly owned subsidiary and agent Defendant Teva USA, manufactures generic drugs for sale and use throughout the United States, including in this judicial district. Teva Ltd. has previously consented to personal jurisdiction in this Court.

NATURE OF THE ACTION

8. This is a civil action concerning the infringement of United States Patent No. 7,960,424 (“the ’424 patent”). This action arises under the patent laws of the United States, 35 U.S.C. §§ 100 *et seq.*, and the Declaratory Judgment Act, 28 U.S.C. §§ 2201-02.

JURISDICTION AND VENUE

9. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a).

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

11. This Court has personal jurisdiction over each of the Defendants by virtue of the fact that, *inter alia*, each Defendant has committed, aided, abetted, contributed to, and/or participated in the commission of a tortious act of patent infringement that has led to foreseeable harm and injury to Plaintiffs. This Court has personal jurisdiction over each of the Defendants for the additional reasons set forth above and below, and for other reasons that will be presented to the Court if such jurisdiction is challenged.

12. This Court has personal jurisdiction over Defendant Reddy Ltd.

13. This Court has personal jurisdiction over Defendant Reddy Inc.
14. This Court has personal jurisdiction over Defendant Sandoz.
15. This Court has personal jurisdiction over Defendant Teva USA.
16. This Court has personal jurisdiction over Defendant Teva Ltd.

THE PATENT

17. On June 14, 2011, the '424 patent, titled "Liquid Pharmaceutical Formulations of Palonosetron," was duly and legally issued to Helsinn and Roche as assignees. A copy of the '424 patent is attached as Exhibit A.

ACTS GIVING RISE TO THIS ACTION

COUNT I – INFRINGEMENT OF THE '424 PATENT BY REDDY

18. Plaintiffs reallege paragraphs 1-17 as if fully set forth herein.
19. Upon information and belief, Defendant Reddy submitted ANDA No. 201533 to the United States Food and Drug Administration ("FDA") under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA No. 201533 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 the '424 patent. ANDA No. 201533 specifically seeks FDA approval to market generic versions 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 '424 patent.
20. ANDA No. 201533 alleges under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '424 patent are invalid.

21. Reddy's submission to the FDA of ANDA No. 201533, including the § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '424 patent under 35 U.S.C. § 271(e)(2)(A).

22. Reddy Ltd. and Reddy Inc. are jointly and severally liable for any infringement of the '424 patent. This is because, upon information and belief, Reddy Ltd. and Reddy Inc. actively and knowingly caused to be submitted, assisted with, participated in, contributed to, and/or directed the submission of ANDA No. 201533 and the § 505(j)(2)(A)(vii)(IV) allegations to the FDA.

23. Reddy's active and knowing participation in, contribution to, aiding, abetting, and/or inducement of the submission to the FDA of ANDA No. 201533 and the § 505(j)(2)(A)(vii)(IV) allegations constitutes infringement of the '424 patent under 35 U.S.C. § 271(e)(2)(A).

24. Plaintiffs are entitled to a declaration that, if Reddy commercially manufactures, uses, offers for sale, 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, Reddy would infringe the '424 patent under 35 U.S.C. § 271(a), (b), and/or (c).

25. Plaintiffs will be irreparably harmed by Reddy'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 '424 PATENT BY SANDOZ

26. Plaintiffs reallege paragraphs 1-25 as if fully set forth herein.

27. Upon information and belief, Defendant Sandoz submitted ANDA No. 202521 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C.

§ 355(j)). ANDA No. 202521 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 the '424 patent. ANDA No. 202521 specifically seeks FDA approval to market generic versions 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 '424 patent.

28. ANDA No. 202521 alleges under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '424 patent are invalid.

29. Sandoz's submission to the FDA of ANDA No. 202521, including the § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '424 patent under 35 U.S.C. § 271(e)(2)(A).

30. Plaintiffs are entitled to a declaration that, if Sandoz commercially manufactures, uses, offers for sale, 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, Sandoz would infringe the '424 patent under 35 U.S.C. § 271(a), (b), and/or (c).

31. Plaintiffs will be irreparably harmed by Sandoz'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 '424 PATENT BY TEVA

32. Plaintiffs reallege paragraphs 1-31 as if fully set forth herein.

33. Upon information and belief, Defendant Teva submitted ANDA No. 090713 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA No. 090713 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 the '424 patent. ANDA No. 090713 specifically seeks FDA approval to market generic versions 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 '424 patent.

34. ANDA No. 090713 alleges under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '424 patent are invalid.

35. Teva's submission to the FDA of ANDA No. 090713, including the § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '424 patent under 35 U.S.C. § 271(e)(2)(A).

36. Teva Ltd. and Teva USA are jointly and severally liable for any infringement of the '424 patent. This is because, upon information and belief, Teva Ltd. and Teva USA actively and knowingly caused to be submitted, assisted with, participated in, contributed to, and/or directed the submission of ANDA No. 090713 and the § 505(j)(2)(A)(vii)(IV) allegations to the FDA.

37. Teva's active and knowing participation in, contribution to, aiding, abetting, and/or inducement of the submission to the FDA of ANDA No. 090713 and the § 505(j)(2)(A)(vii)(IV) allegations constitutes infringement of the '424 patent under 35 U.S.C. § 271(e)(2)(A).

38. Plaintiffs are entitled to a declaration that, if Teva commercially manufactures, uses, offers for sale, 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, Teva would infringe the '424 patent under 35 U.S.C. § 271(a), (b), and/or (c).

39. Plaintiffs will be irreparably harmed by Teva'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 Defendants Reddy Ltd., Reddy Inc., Sandoz, Teva USA, and Teva Ltd. have infringed the '424 patent by submitting the aforesaid ANDAs;

B. An Order be issued pursuant to 35 U.S.C. § 271(e)(4)(A) that the effective date of any approval of any of Defendants' ANDAs identified in this Complaint be a date that is not earlier than the expiration date of the '424 patent, or any later expiration of exclusivity for the '424 patent to which Plaintiffs are or become entitled;

C. An Order be issued that Defendants Reddy Ltd., Reddy Inc., Sandoz, Teva USA, and Teva Ltd., their officers, agents, servants and employees, and those persons in active concert or participation with any of them, are preliminarily and permanently enjoined from commercially manufacturing, using, offering for sale, importing, or selling 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 '424 patent, prior to the expiration of the '424 patent, 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: September 23, 2011

Respectfully submitted,

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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 matter captioned *Helsinn Healthcare S.A., et al. v. Dr. Reddy Laboratories, Ltd., et al.*, Civil Action No. 11-3962 (MLC)(DEA), is related to the matter in controversy because the matter in controversy involves the same plaintiffs, same defendants, same ANDAs, and in both cases, 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: September 23, 2011

Respectfully submitted,

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**UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY**

HEL SINN HEALTHCARE S.A. and
ROCHE PALO ALTO LLC,

Plaintiffs,

v.

DR. REDDY'S LABORATORIES, LTD. and
DR. REDDY'S LABORATORIES, INC.,

Defendants.

Civil Action No. _____

**COMPLAINT FOR
PATENT INFRINGEMENT**

(Filed Electronically)

Plaintiffs Helsinn Healthcare S.A. (“Helsinn”) and Roche Palo Alto LLC (“Roche”), for their Complaint against Defendants Dr. Reddy’s Laboratories, Ltd. (“Reddy Ltd.”) and Dr. Reddy’s Laboratories, Inc. (“Reddy Inc.”), hereby allege as follows:

THE PARTIES

1. Plaintiff Helsinn is a Swiss corporation having a principal place of business at Via Pian Scairolo, 9, CH-6912 Lugano-Pazzallo, Switzerland.
2. Plaintiff 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, Defendant Reddy Ltd. is an Indian corporation having a principal place of business at 7-1-27, Ameerpet, Hyderabad, Andhra Pradesh, India. Upon information and belief, Reddy Ltd., itself and through its wholly owned subsidiary and agent Defendant Reddy Inc. (referred to collectively as “Reddy”), manufactures generic drugs for sale and use throughout the United States, including in this Judicial District. In its March 30, 2012 notice letter addressed to Helsinn and Roche, Reddy Ltd. appointed Lee Banks, Esq. of Reddy Inc., 200 Somerset Corporate Boulevard, Floor 7, Bridgewater, New Jersey 08807, as its agent in New Jersey authorized to accept service of process for purposes of the subject matter at issue in this action. Reddy Ltd. has previously consented to personal jurisdiction in this Court, including in the related actions *Helsinn Healthcare S.A., et al. v. Dr. Reddy’s Laboratories, Ltd., et al.*, Civil Action No. 11-3962 (MLC)(DEA), and *Helsinn Healthcare S.A., et al. v. Dr. Reddy’s Laboratories, Ltd., et al.*, Civil Action No. 11-5579 (MLC)(DEA), the latter of which was consolidated with Civil Action No. 11-3962.
4. Upon information and belief, Defendant Reddy Inc. is a corporation organized and existing under the laws of the State of New Jersey, having a principal place of

business at 200 Somerset Corporate Boulevard, Floor 7, Bridgewater, New Jersey 08807, and is a wholly owned subsidiary and agent of Defendant Reddy Ltd. Upon information and belief, Reddy Inc. is registered to do business in New Jersey and does business in this Judicial District. In its March 30, 2012 notice letter addressed to Helsinn and Roche, Reddy Inc. appointed Lee Banks, Esq. of Reddy Inc., 200 Somerset Corporate Boulevard, Floor 7, Bridgewater, New Jersey 08807, as its agent in New Jersey authorized to accept service of process for purposes of the subject matter at issue in this action. Reddy Inc. has previously consented to personal jurisdiction in this Court, including in the related actions *Helsinn Healthcare S.A., et al. v. Dr. Reddy's Laboratories, Ltd., et al.*, Civil Action No. 11-3962 (MLC)(DEA), and *Helsinn Healthcare S.A., et al. v. Dr. Reddy's Laboratories, Ltd., et al.*, Civil Action No. 11-5579 (MLC)(DEA), the latter of which was consolidated with Civil Action No. 11-3962.

NATURE OF THE ACTION

5. This is a civil action concerning the infringement of United States Patent No. 7,947,724 (“the ’724 patent”). This action arises under the patent laws of the United States, 35 U.S.C. §§ 100 *et seq.*, and the Declaratory Judgment Act, 28 U.S.C. §§ 2201-02.

JURISDICTION AND VENUE

6. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a).

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

8. This Court has personal jurisdiction over each of the Defendants by virtue of the fact that, *inter alia*, each Defendant has committed, aided, abetted, contributed to, and/or participated in the commission of a tortious act of patent infringement that has led to foreseeable harm and injury to Plaintiffs. This Court has personal jurisdiction over each of the Defendants

for the additional reasons set forth above and below, and for other reasons that will be presented to the Court if such jurisdiction is challenged.

9. This Court has personal jurisdiction over Defendant Reddy Ltd.

10. This Court has personal jurisdiction over Defendant Reddy Inc.

THE PATENT

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

ACTS GIVING RISE TO THIS ACTION

INFRINGEMENT OF THE '724 PATENT BY REDDY

12. Plaintiffs reallege paragraphs 1-11 as if fully set forth herein.

13. Upon information and belief, Defendants submitted NDA No. 203050 to the United States Food and Drug Administration ("FDA") under § 505(b)(2) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(b)(2)). NDA No. 203050 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 the '724 patent. NDA No. 203050 specifically seeks FDA approval to market and sell generic versions 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.

14. NDA No. 203050 alleges under § 505(b)(2)(A)(iv) of the Federal Food, Drug and Cosmetic Act that the claims of the '724 patent are not infringed.

15. Defendants' submission to the FDA of NDA No. 203050, including the § 505(b)(2)(A)(iv) allegations, constitutes infringement of the '724 patent under 35 U.S.C. § 271(e)(2)(A).

16. Defendants are jointly and severally liable for any infringement of the '724 patent. This is because, upon information and belief, Defendants actively and knowingly caused to be submitted, assisted with, participated in, contributed to, and/or directed the submission of NDA No. 203050 and the § 505(b)(2)(A)(iv) allegations to the FDA.

17. Defendants' active and knowing participation in, contribution to, aiding, abetting, and/or inducement of the submission to the FDA of NDA No. 203050 and the § 505(b)(2)(A)(iv) allegations constitutes infringement of the '724 patent under 35 U.S.C. § 271(e)(2)(A).

18. Plaintiffs are entitled to a declaration that, if Defendants commercially manufacture, use, offer for sale, or sell their 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, Defendants would infringe the '724 patent under 35 U.S.C. § 271(a), (b), and/or (c).

19. Plaintiffs will be irreparably harmed by Defendants' 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 Defendants have infringed the '724 patent by submitting the aforesaid NDA;

B. An Order be issued pursuant to 35 U.S.C. § 271(e)(4)(A) that the effective date of any approval of any of Defendants' NDA identified in this Complaint be a date that is not earlier than the expiration date of the '724 patent, or any later expiration of exclusivity for the '724 patent to which Plaintiffs are or become entitled;

C. An Order be issued that Defendants, their officers, agents, servants and employees, and those persons in active concert or participation with any of them, are preliminarily and permanently enjoined from commercially manufacturing, using, offering for sale, importing, or selling 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 patent, prior to the expiration of the '724 patent, 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: May 11, 2012

Respectfully submitted,

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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 matter captioned *Helsinn Healthcare S.A., et al. v. Dr. Reddy Laboratories, Ltd., et al.*, Civil Action No. 11-3962 (MLC)(DEA), is related to the matter in controversy because the matter in controversy involves the same plaintiffs, the common defendants Dr. Reddy's Laboratories, Ltd. and Dr. Reddy's Laboratories, Inc. ("Reddy"), one of the same patents, and in both cases, Reddy is seeking FDA approval to market a generic version of the same pharmaceutical product.

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: May 11, 2012

Respectfully submitted,

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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 Mikszal**, 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.

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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

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LIQUID PHARMACEUTICAL FORMULATIONS OF PALONOSETRON

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

BACKGROUND OF THE INVENTION

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

Emesis is a devastating consequence of cytotoxic therapy, radiotherapy, and post-operative environments that drastically affects the quality of life of people undergoing such treatments. In recent years a class of drugs referred to as 5-HT₃ (5-hydroxytryptamine) receptor antagonists has been developed that treat such emesis by antagonizing cerebral functions associated with the 5-HT₃ receptor. See *Drugs Acting on 5-Hydroxytryptamine Receptors*: The Lancet Sep. 23, 1989 and references cited therein. Drugs within this class include ondansetron, granisetron, alosetron, tropisetron, and dolasetron. These 5-HT₃ antagonists are often administered intravenously shortly before chemotherapy or radiotherapy is initiated, and can be administered more than once during a cycle of chemotherapy or radiotherapy. In addition, they are often supplied as tablets or oral elixirs to either supplement an intravenous administration, or to ease home usage of the drug if the patient is self-administering the chemotherapeutic regimen.

Because some chemotherapeutic agents can induce emesis over extended periods of several days even when they are administered only once, it would be desirable to administer an emesis-inhibiting drug such as a 5-HT₃ antagonist every day until the risk of emesis has substantially subsided. The present class of 5-HT₃ antagonists has not proven especially helpful meeting this need, however, because the 5-HT₃ receptor antagonists currently marketed have proven to be less effective in controlling delayed nausea and vomiting than they are at controlling acute emesis. Sabra, K, *Choice of a 5HT₃ Receptor Antagonist for the Hospital Formulary*. EHP, October 1996;2 (suppl 1):S19-24.

Recently, clinical investigations have been made concerning palonosetron, a new 5-HT₃ 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-HT₃ 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-HT₃ 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 1/10th the amount of other previously known compounds for treating emesis, which surprisingly allows the use of concentrations of palonosetron far below

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

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

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

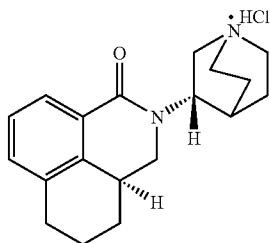
DETAILED DESCRIPTION OF THE INVENTION

Definitions

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

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

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



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

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

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

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

EXAMPLES

Example 1

Stabilizing pH

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

Example 2

Stabilizing Concentration Ranges

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

Example 3

Tonicifying Agent

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

Example 4

Formulation I

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

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

*calculated as a free base

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Example 5

Formulation II

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

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

*calculated as a free base

Example 6

Stability of Palonosetron without Dexamethasone

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

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

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

Example 7

Stability of Palonosetron with Dexamethasone

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

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

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

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

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

What is claimed is:

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

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

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

3. The solution of claim 1 comprising palonosetron hydrochloride.

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

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

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

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

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

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

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

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

10. The solution of claim 8 comprising palonosetron hydrochloride.

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

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

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

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

* * * * *

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**UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY**

HEL SINN HEALTHCARE S.A. and
ROCHE PALO ALTO LLC,

Plaintiffs,

v.

DR. REDDY'S LABORATORIES, LTD.,
DR. REDDY'S LABORATORIES, INC.,
SANDOZ INC., TEVA PHARMACEUTICALS
USA, INC., and TEVA PHARMACEUTICAL
INDUSTRIES, LTD.,

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 its Complaint against Defendants Dr. Reddy’s Laboratories, Ltd. (“Reddy Ltd.”), Dr. Reddy’s Laboratories, Inc. (“Reddy Inc.”), Sandoz Inc. (“Sandoz”), Teva Pharmaceuticals USA, Inc. (“Teva USA”), and Teva Pharmaceutical Industries, Ltd. (“Teva Ltd.”), hereby allege as follows:

THE PARTIES

1. Plaintiff Helsinn is a Swiss corporation having its principal place of business at Via Pian Scairolo, 9, CH-6912 Lugano-Pazzallo, Switzerland.
2. Plaintiff 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, Defendant Reddy Ltd. is an Indian corporation having a place of business at 7-1-27, Ameerpet, Hyderabad, Andhra Pradesh, India. Upon information and belief, Reddy Ltd., itself and through its wholly owned subsidiary and agent Defendant Reddy Inc. (referred to collectively as “Reddy”), manufactures generic drugs for sale and use throughout the United States, including in this judicial district. Reddy Ltd. has previously consented to personal jurisdiction in this Court, including in the related actions *Helsinn Healthcare S.A., et al. v. Dr. Reddy’s Laboratories, Ltd., et al.*, Civil Action No. 11-3962 (MLC)(DEA) and *Helsinn Healthcare S.A., et al. v. Dr. Reddy’s Laboratories, Ltd., et al.*, Civil Action No. 11-5579 (MLC)(DEA), the latter of which was consolidated with Civil Action No. 11-3962, and another related action *Helsinn Healthcare S.A., et al. v. Dr. Reddy’s Laboratories, Ltd., et al.*, Civil Action No. 12-2867 (MLC)(DEA).
4. Upon information and belief, Defendant Reddy Inc. is a corporation organized and existing under the laws of the State of New Jersey, having a place of business at

200 Somerset Corporate Boulevard, Floor 7, Bridgewater, New Jersey 08807, and is a wholly owned subsidiary and agent of Defendant Reddy Ltd. Upon information and belief, Reddy Inc. is registered to do business in New Jersey and does business in this judicial district. Reddy Inc. has previously consented to personal jurisdiction in this Court, including in the related actions *Helsinn Healthcare S.A., et al. v. Dr. Reddy's Laboratories, Ltd., et al.*, Civil Action No. 11-3962 (MLC)(DEA) and *Helsinn Healthcare S.A., et al. v. Dr. Reddy's Laboratories, Ltd., et al.*, Civil Action No. 11-5579 (MLC)(DEA), the latter of which was consolidated with Civil Action No. 11-3962, and another related action *Helsinn Healthcare S.A., et al. v. Dr. Reddy's Laboratories, Ltd., et al.*, Civil Action No. 12-2867 (MLC)(DEA).

5. Upon information and belief, Defendant Sandoz is a corporation organized and existing under the laws of the State of Colorado, having a place of business at 506 Carnegie Center, Suite 400, Princeton, New Jersey 08540. Upon information and belief, Sandoz is registered to do business in New Jersey and does business in this judicial district. Sandoz has previously consented to personal jurisdiction in this Court, including in the related actions *Helsinn Healthcare S.A., et al. v. Dr. Reddy's Laboratories, Ltd., et al.*, Civil Action No. 11-3962 (MLC)(DEA) and *Helsinn Healthcare S.A., et al. v. Dr. Reddy's Laboratories, Ltd., et al.*, Civil Action No. 11-5579 (MLC)(DEA), the latter of which was consolidated with Civil Action No. 11-3962.

6. Upon information and belief, Defendant Teva USA is a corporation organized and existing under the laws of the State of Delaware, having a place of business at 400 Chestnut Ridge Road, Woodcliff Lake, New Jersey 07677. Teva USA is a wholly owned subsidiary and agent of Defendant Teva Ltd. (referred to collectively as "Teva"). Upon information and belief, Teva USA has facilities in New Jersey, is registered to do business in New Jersey, and does business in this judicial district. Teva USA has previously consented to

personal jurisdiction in this Court, including in the related actions *Helsinn Healthcare S.A., et al. v. Dr. Reddy's Laboratories, Ltd., et al.*, Civil Action No. 11-3962 (MLC)(DEA) and *Helsinn Healthcare S.A., et al. v. Dr. Reddy's Laboratories, Ltd., et al.*, Civil Action No. 11-5579 (MLC)(DEA), the latter of which was consolidated with Civil Action No. 11-3962.

7. Upon information and belief, Defendant Teva Ltd. is an Israeli corporation having a place of business at 5 Basel Street, Petah Tikva 49131, Israel. Upon information and belief, Teva Ltd., itself and through its wholly owned subsidiary and agent Defendant Teva USA, manufactures generic drugs for sale and use throughout the United States, including in this judicial district. Teva Ltd. has previously consented to personal jurisdiction in this Court, including in the related actions *Helsinn Healthcare S.A., et al. v. Dr. Reddy's Laboratories, Ltd., et al.*, Civil Action No. 11-3962 (MLC)(DEA) and *Helsinn Healthcare S.A., et al. v. Dr. Reddy's Laboratories, Ltd., et al.*, Civil Action No. 11-5579 (MLC)(DEA), the latter of which was consolidated with Civil Action No. 11-3962.

NATURE OF THE ACTION

8. This is a civil action concerning the infringement of United States Patent No. 8,518,981 (“the ’981 patent”). 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

9. 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.

10. 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.

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

12. This Court has personal jurisdiction over each of the Defendants by virtue of the fact that, *inter alia*, each Defendant has committed, aided, abetted, contributed to, and/or participated in the commission of a tortious act of patent infringement that has led to foreseeable harm and injury to Plaintiffs. This Court has personal jurisdiction over each of the Defendants for the additional reasons set forth above and below, and for other reasons that will be presented to the Court if such jurisdiction is challenged.

13. This Court has personal jurisdiction over Defendant Reddy Ltd.

14. This Court has personal jurisdiction over Defendant Reddy Inc.

15. This Court has personal jurisdiction over Defendant Sandoz.

16. This Court has personal jurisdiction over Defendant Teva USA.

17. This Court has personal jurisdiction over Defendant Teva Ltd.

THE PATENTS

18. On August 27, 2013, the '981 patent, titled "Liquid Pharmaceutical Formulations of Palonosetron," was duly and legally issued to Plaintiffs as assignees. A copy of the '981 patent is attached as Exhibit A.

19. Pursuant to 21 U.S.C. § 355(b)(1), the '981 patent is 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 0.25 mg / 5 mL and 0.075 mg / 1.5 mL palonosetron hydrochloride intravenous solutions.

ACTS GIVING RISE TO THIS ACTION

COUNT I – INFRINGEMENT OF THE '981 PATENT BY REDDY'S ANDA

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

21. Upon information and belief, Reddy submitted ANDA No. 201533 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA No. 201533 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 the '981 patent. ANDA No. 201533 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 '981 patent.

22. The '981 patent had not been issued at the time Reddy made its § 505(j)(2)(A)(vii)(IV) certification regarding Plaintiffs' other Orange Book-listed patents.

23. Upon information and belief, Reddy has been aware of the existence of the '981 patent since at least as early as September 3, 2013, and is required by law to either amend its ANDA to contain a § 505(j)(2)(A)(vii)(IV) certification with respect to the '981 patent, or must relinquish its request that the FDA approve ANDA No. 201533 prior to the expiration of Plaintiffs' Orange Book-listed patents.

24. Reddy continues to seek approval of ANDA No. 201533 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 '981 patent.

25. By seeking approval of its ANDA 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 the '981 patent, Reddy has infringed that patent pursuant to 35 U.S.C. § 271(e)(2)(A).

26. Reddy Ltd. and Reddy Inc. are jointly and severally liable for any infringement of the '981 patent. This is because, upon information and belief, Reddy Ltd. and Reddy Inc. actively and knowingly caused to be submitted, assisted with, participated in, contributed to, and/or directed the submission of ANDA No. 201533 to the FDA.

27. Reddy's active and knowing participation in, contribution to, aiding, abetting, and/or inducement of the submission to the FDA of ANDA No. 201533 constitutes infringement of the '981 patent under 35 U.S.C. § 271(e)(2)(A).

28. Plaintiffs are entitled to a declaration that, if Reddy commercially manufactures, uses, offers for sale, 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, Reddy would infringe the '981 patent under 35 U.S.C. § 271(a), (b), and/or (c).

29. Plaintiffs will be irreparably harmed by Reddy'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 '981 PATENT
BY REDDY'S 505(b)(2) APPLICATION**

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

31. Upon information and belief, Reddy submitted NDA No. 203050 to the FDA under § 505(b)(2) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(b)(2)). NDA No. 203050 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 the '981 patent.

NDA No. 203050 specifically seeks FDA approval to market and sell generic versions 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 '981 patent.

32. The '981 patent had not issued at the time Reddy made its § 505(b)(2)(A)(iv) certification regarding Plaintiffs' other Orange Book-listed patents.

33. Upon information and belief, Reddy has been aware of the existence of the '981 patent since at least as early as September 3, 2013, and is required by law to either amend its ANDA to contain a § 505(b)(2)(A)(iv) certification with respect to the '981 patent, or must relinquish its request that the FDA approve NDA No. 203050 prior to the expiration of Plaintiffs' Orange Book-listed patents.

34. Reddy continues to seek approval of NDA No. 203050 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 '981 patent.

35. By seeking approval of its NDA 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 the '981 patent, Reddy has infringed that patent pursuant to 35 U.S.C. § 271(e)(2)(A).

36. Reddy Ltd. and Reddy Inc. are jointly and severally liable for any infringement of the '981 patent. This is because, upon information and belief, Reddy Ltd. and Reddy Inc. actively and knowingly caused to be submitted, assisted with, participated in, contributed to, and/or directed the submission of NDA No. 203050 to the FDA.

37. Reddy's active and knowing participation in, contribution to, aiding, abetting, and/or inducement of the submission to the FDA of NDA No. 203050 constitutes infringement of the '981 patent under 35 U.S.C. § 271(e)(2)(A).

38. Plaintiffs are entitled to a declaration that, if Reddy commercially manufactures, uses, offers for sale, 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, Reddy would infringe the '981 patent under 35 U.S.C. § 271(a), (b), and/or (c).

39. Plaintiffs will be irreparably harmed by Reddy'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 '981 PATENT BY SANDOZ'S ANDA

40. Plaintiffs reallege paragraphs 1-39 as if fully set forth herein.

41. Upon information and belief, Sandoz submitted ANDA No. 202521 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA No. 202521 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 the '981 patent. ANDA No. 202521 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 '981 patent.

42. The '981 patent had not been issued at the time Sandoz made its § 505(j)(2)(A)(vii)(IV) certification regarding Plaintiffs' other Orange Book-listed patents.

43. Upon information and belief, Sandoz has been aware of the existence of the '981 patent since at least as early as September 3, 2013, and is required by law to either

amend its ANDA to contain a § 505(j)(2)(A)(vii)(IV) certification with respect to the '981 patent, or must relinquish its request that the FDA approve ANDA No. 202521 prior to the expiration of Plaintiffs' Orange Book-listed patents.

44. Sandoz continues to seek approval of ANDA No. 202521 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 '981 patent.

45. By seeking approval of its ANDA 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 the '981 patent, Sandoz has infringed that patent pursuant to 35 U.S.C. § 271(e)(2)(A).

46. Sandoz's active and knowing participation in, contribution to, aiding, abetting, and/or inducement of the submission to the FDA of ANDA No. 202521 constitutes infringement of the '981 patent under 35 U.S.C. § 271(e)(2)(A).

47. Plaintiffs are entitled to a declaration that, if Sandoz commercially manufactures, uses, offers for sale, 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, Sandoz would infringe the '981 patent under 35 U.S.C. § 271(a), (b), and/or (c).

48. Plaintiffs will be irreparably harmed by Sandoz'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 '981 PATENT BY TEVA'S ANDA

49. Plaintiffs reallege paragraphs 1-48 as if fully set forth herein.

50. Upon information and belief, Teva submitted ANDA No. 090713 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA No. 090713 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 the '981 patent. ANDA No. 090713 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 '981 patent.

51. The '981 patent had not been issued at the time Teva made its § 505(j)(2)(A)(vii)(IV) certification regarding Plaintiffs' other Orange Book-listed patents.

52. Upon information and belief, Teva has been aware of the existence of the '981 patent since at least as early as September 3, 2013, and is required by law to either amend its ANDA to contain a § 505(j)(2)(A)(vii)(IV) certification with respect to the '981 patent, or must relinquish its request that the FDA approve ANDA No. 090713 prior to the expiration of Plaintiffs' Orange Book-listed patents.

53. Teva continues to seek approval of ANDA No. 090713 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 '981 patent.

54. By seeking approval of its ANDA 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 the '981 patent, Teva has infringed that patent pursuant to 35 U.S.C. § 271(e)(2)(A).

55. Teva USA and Teva Ltd. are jointly and severally liable for any infringement of the '981 patent. This is because, upon information and belief, Teva USA and Teva Ltd. actively and knowingly caused to be submitted, assisted with, participated in, contributed to, and/or directed the submission of ANDA No. 090713 to the FDA.

56. Teva's active and knowing participation in, contribution to, aiding, abetting, and/or inducement of the submission to the FDA of ANDA No. 090713 constitutes infringement of the '981 patent under 35 U.S.C. § 271(e)(2)(A).

57. Plaintiffs are entitled to a declaration that, if Teva commercially manufactures, uses, offers for sale, 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, Teva would infringe the '981 patent under 35 U.S.C. § 271(a), (b), and/or (c).

58. Plaintiffs will be irreparably harmed by Teva'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 Defendants Reddy Ltd., Reddy Inc., Sandoz, Teva USA, and Teva Ltd. have infringed the '981 patent by submitting the aforesaid ANDAs;

B. A Judgment be entered declaring that Defendants Reddy Ltd. and Reddy Inc. have infringed the '981 patent by submitting the aforesaid NDA;

C. An Order be issued pursuant to 35 U.S.C. § 271(e)(4)(A) that the effective date of any approval of any of Defendants' ANDAs identified in this Complaint be a date that is

not earlier than the expiration date of the '981 patent, or any later expiration of exclusivity for the '981 patent to which Plaintiffs are or become entitled;

D. An Order be issued pursuant to 35 U.S.C. § 271(e)(4)(A) that the effective date of any approval of Defendants Reddy Ltd. and Reddy Inc.'s NDA identified in this Complaint be a date that is not earlier than the expiration date of the '981 patent, or any later expiration of exclusivity for the '981 patent to which Plaintiffs are or become entitled;

E. An Order be issued that Defendants Reddy Ltd., Reddy Inc., Sandoz, Teva USA, and Teva Ltd., their officers, agents, servants and employees, and those persons in active concert or participation with any of them, are preliminarily and permanently enjoined from commercially manufacturing, using, offering for sale, importing, or selling 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 '981 patent, prior to the expiration of the '981 patent, including any extensions to which Plaintiffs are or become entitled; and

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

Dated: September 30, 2013

Respectfully submitted,

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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) and *Helsinn Healthcare S.A., et al. v. Dr. Reddy Laboratories, Ltd., et al.*, Civil Action No. 12-2867 (MLC)(DEA), are related to the matter in controversy because the matter in controversy involves the same plaintiffs, same defendants, and, in both cases, 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: September 30, 2013

Respectfully submitted,

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EXHIBIT A



US008518981B2

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

(10) **Patent No.:** **US 8,518,981 B2**
(45) **Date of Patent:** ***Aug. 27, 2013**

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

(75) Inventors: **Giorgio Calderari**, Rancate (CH); **Daniele Bonadeo**, Varese (IT); **Roberta Cannella**, Varese (IT); **Andrew Mikszal**, Palo Alto, CA (US); **Thomas Malefy**, Carmel Valley, CA (US); **Kathleen Lee**, Palo Alto, CA (US)

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2001/0020029	A1	9/2001	James
2003/0095926	A1	5/2003	Dugger, III

(73) Assignees: **Helsinn Healthcare SA**, Lugano/Pazzallo (CH); **Roche Palo Alto LLC**, Palo Alto, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **13/087,012**

(22) Filed: **Apr. 14, 2011**

(65) **Prior Publication Data**

US 2011/0192493 A1 Aug. 11, 2011

Related U.S. Application Data

(63) 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.

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

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(57) **ABSTRACT**

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

12 Claims, No Drawings

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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).

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**LIQUID PHARMACEUTICAL
FORMULATIONS OF PALONOSETRON**

The present application is a continuation of U.S. Ser. No. 11/186,311 filed Jul. 21, 2005 (allowed), 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-HT₃ (5-hydroxytryptamine) receptor antagonists has been developed that treat such emesis by antagonizing cerebral functions associated with the 5-HT₃ receptor. See *Drugs Acting on 5-Hydroxytryptamine Receptors*: The Lancet Sep. 23, 1989 and references cited therein. Drugs within this class include ondansetron, granisetron, alosetron, tropisetron, and dolasetron. These 5-HT₃ antagonists are often administered intravenously shortly before chemotherapy or radiotherapy is initiated, and can be administered more than once during a cycle of chemotherapy or radiotherapy. In addition, they are often supplied as tablets or oral elixirs to either supplement an intravenous administration, or to ease home usage of the drug if the patient is self-administering the chemotherapeutic regimen.

Because some chemotherapeutic agents can induce emesis over extended periods of several days even when they are administered only once, it would be desirable to administer an emesis-inhibiting drug such as a 5-HT₃ antagonist every day until the risk of emesis has substantially subsided. The present class of 5-HT₃ antagonists has not proven especially helpful meeting this need, however, because the 5-HT₃ receptor antagonists currently marketed have proven to be less effective in controlling delayed nausea and vomiting than they are at controlling acute emesis. Sabra, K. *Choice of a 5HT₃ Receptor Antagonist for the Hospital Formulary*. EHP, October 1996; 2 (suppl 1):S19-24.

Recently, clinical investigations have been made concerning palonosetron, a new 5-HT₃ 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-HT₃ 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

-continued

Ingredient	Mg
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-HT₃ 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

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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

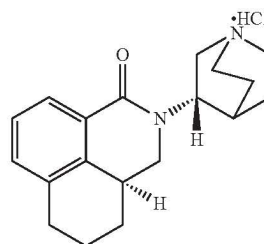
Definitions

"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:

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

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

"Pharmaceutically acceptable salts" means salts which are pharmaceutically acceptable, as defined above, and which possess the desired pharmacological activity. Such salts include acid addition salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or with organic acids such as acetic acid, propionic acid, hexanoic acid, heptanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, o-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedithionyl sulfonic 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 $\frac{1}{10}^{th}$ 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 embodi-

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ments, 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

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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 e) 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

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containers (preferably 5 ml. vials); h) 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

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-continued

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

*calculated as a free base

Example 5

Formulation II

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

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

*calculated as a free base

Example 6

Stability of Palonosetron without Dexamethasone

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

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

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

Example 7

Stability of Palonosetron with Dexamethasone

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

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

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

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

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 of manufacturing and terminally sterilizing a finished single unit dose vial of palonosetron or a pharmaceutically acceptable salt thereof comprising: a) providing one or more sterile open containers; b) filling said containers with a pharmaceutically stable solution of palonosetron or a phar-

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maceutically acceptable salt thereof; c) sealing said filled containers; d) terminally sterilizing said sealed, filled containers; and e) optionally adjusting the pH of said solution using HCl or NaOH prior to step (c), wherein the pharmaceutically stable solution has a pH of from about 4.0 to about 6.0 and comprises palonosetron hydrochloride in a concentration of from about 0.03 mg/mL to about 0.2 mg/mL based on the weight of the free base, an aqueous carrier, and a tonicity agent, and wherein the pharmaceutically stable solution optionally comprises one or a combination of mannitol, a chelating agent, and a citrate buffer.

2. The method of claim 1, wherein said solution comprises 0.05 mg/ml of palonosetron hydrochloride based on the weight of the free base.

3. The method of claim 1, wherein said solution comprises HCl or NaOH as a pH adjusting agent.

4. The method of claim 1, wherein said solution has a pH of from 4.5 to 5.5, HCl or NaOH as a pH adjusting agent, and mannitol.

5. A single unit dose of palonosetron hydrochloride made by the method of claim 4.

6. The method of claim 1, wherein said solution has a pH of from 4.5 to 5.5, HCl or NaOH as a pH adjusting agent, a chelating agent and mannitol.

7. A single unit dose of palonosetron hydrochloric made by the method of claim 6.

8. The method of claim 1, wherein said solution comprises HCl or NaOH as a pH adjusting agent, a chelating agent and mannitol.

9. The method of claim 1, wherein said solution comprises a chelating agent and mannitol.

10. The method of claim 1, wherein said solution comprises a chelating agent.

11. The method of claim 1, wherein said solution comprises mannitol.

12. A single unit dose of palonosetron hydrochloride made by the method of claim 1.

* * * * *

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**UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY**

HEL SINN HEALTHCARE S.A. and
ROCHE PALO ALTO LLC,

Plaintiffs,

v.

DR. REDDY'S LABORATORIES, LTD.,
DR. REDDY'S LABORATORIES, INC.,
SANDOZ INC., TEVA PHARMACEUTICALS
USA, INC., and TEVA PHARMACEUTICAL
INDUSTRIES, LTD.,

Defendants.

Civil Action No. 13-5815 (MLC)(DEA)

**AMENDED COMPLAINT FOR
PATENT INFRINGEMENT**

(Filed Electronically)

Plaintiffs Helsinn Healthcare S.A. (“Helsinn”) and Roche Palo Alto LLC (“Roche”) (collectively, “Plaintiffs”), for their Complaint against Defendants Dr. Reddy’s Laboratories, Ltd. (“Reddy Ltd.”), Dr. Reddy’s Laboratories, Inc. (“Reddy Inc.”), Sandoz Inc. (“Sandoz”), Teva Pharmaceuticals USA, Inc. (“Teva USA”), and Teva Pharmaceutical Industries, Ltd. (“Teva Ltd.”) (collectively, “Defendants”), hereby allege as follows:

THE PARTIES

1. Plaintiff Helsinn is a Swiss corporation having its principal place of business at Via Pian Scairolo, 9, CH-6912 Lugano-Pazzallo, Switzerland.
2. Plaintiff 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, Defendant Reddy Ltd. is an Indian corporation having a place of business at 7-1-27, Ameerpet, Hyderabad, Andhra Pradesh, India. Upon information and belief, Reddy Ltd., itself and through its wholly owned subsidiary and agent Defendant Reddy Inc. (referred to collectively as “Reddy”), manufactures generic drugs for sale and use throughout the United States, including in this judicial district. Reddy Ltd. has previously consented to personal jurisdiction in this Court, including in the related actions *Helsinn Healthcare S.A., et al. v. Dr. Reddy’s Laboratories, Ltd., et al.*, Civil Action No. 11-3962 (MLC)(DEA) and *Helsinn Healthcare S.A., et al. v. Dr. Reddy’s Laboratories, Ltd., et al.*, Civil Action No. 11-5579 (MLC)(DEA), the latter of which was consolidated with Civil Action No. 11-3962, and another related action *Helsinn Healthcare S.A., et al. v. Dr. Reddy’s Laboratories, Ltd., et al.*, Civil Action No. 12-2867 (MLC)(DEA). Reddy Ltd. has also consented to personal jurisdiction for purposes of this action.

4. Upon information and belief, Defendant Reddy Inc. is a corporation organized and existing under the laws of the State of New Jersey, having a place of business at 200 Somerset Corporate Boulevard, Floor 7, Bridgewater, New Jersey 08807, and is a wholly owned subsidiary and agent of Defendant Reddy Ltd. Upon information and belief, Reddy Inc. is registered to do business in New Jersey and does business in this judicial district. Reddy Inc. has previously consented to personal jurisdiction in this Court, including in the related actions *Helsinn Healthcare S.A., et al. v. Dr. Reddy's Laboratories, Ltd., et al.*, Civil Action No. 11-3962 (MLC)(DEA) and *Helsinn Healthcare S.A., et al. v. Dr. Reddy's Laboratories, Ltd., et al.*, Civil Action No. 11-5579 (MLC)(DEA), the latter of which was consolidated with Civil Action No. 11-3962, and another related action *Helsinn Healthcare S.A., et al. v. Dr. Reddy's Laboratories, Ltd., et al.*, Civil Action No. 12-2867 (MLC)(DEA). Reddy Inc. has also consented to personal jurisdiction for purposes of this action.

5. Upon information and belief, Defendant Sandoz is a corporation organized and existing under the laws of the State of Colorado, having a place of business at 506 Carnegie Center, Suite 400, Princeton, New Jersey 08540. Upon information and belief, Sandoz is registered to do business in New Jersey and does business in this judicial district. Sandoz has previously consented to personal jurisdiction in this Court, including in the related actions *Helsinn Healthcare S.A., et al. v. Dr. Reddy's Laboratories, Ltd., et al.*, Civil Action No. 11-3962 (MLC)(DEA) and *Helsinn Healthcare S.A., et al. v. Dr. Reddy's Laboratories, Ltd., et al.*, Civil Action No. 11-5579 (MLC)(DEA), the latter of which was consolidated with Civil Action No. 11-3962. Sandoz has also consented to personal jurisdiction for purposes of this action.

6. Upon information and belief, Defendant Teva USA is a corporation organized and existing under the laws of the State of Delaware, having a place of business at 400 Chestnut Ridge Road, Woodcliff Lake, New Jersey 07677. Teva USA is a wholly owned

subsidiary and agent of Defendant Teva Ltd. (referred to collectively as “Teva”). Upon information and belief, Teva USA has facilities in New Jersey, is registered to do business in New Jersey, and does business in this judicial district. Teva USA has previously consented to personal jurisdiction in this Court, including in the related actions *Helsinn Healthcare S.A., et al. v. Dr. Reddy’s Laboratories, Ltd., et al.*, Civil Action No. 11-3962 (MLC)(DEA) and *Helsinn Healthcare S.A., et al. v. Dr. Reddy’s Laboratories, Ltd., et al.*, Civil Action No. 11-5579 (MLC)(DEA), the latter of which was consolidated with Civil Action No. 11-3962. Teva USA has also consented to personal jurisdiction for purposes of this action.

7. Upon information and belief, Defendant Teva Ltd. is an Israeli corporation having a place of business at 5 Basel Street, Petah Tikva 49131, Israel. Upon information and belief, Teva Ltd., itself and through its wholly owned subsidiary and agent Defendant Teva USA, manufactures generic drugs for sale and use throughout the United States, including in this judicial district. Teva Ltd. has previously consented to personal jurisdiction in this Court, including in the related actions *Helsinn Healthcare S.A., et al. v. Dr. Reddy’s Laboratories, Ltd., et al.*, Civil Action No. 11-3962 (MLC)(DEA) and *Helsinn Healthcare S.A., et al. v. Dr. Reddy’s Laboratories, Ltd., et al.*, Civil Action No. 11-5579 (MLC)(DEA), the latter of which was consolidated with Civil Action No. 11-3962. Teva Ltd. has also consented to personal jurisdiction for purposes of this action.

NATURE OF THE ACTION

8. This is a civil action concerning the infringement of United States Patent No. 8,518,981 (“the ’981 patent”), United States Patent No. 8,598,218 (“the ’218 patent”), and United States Patent No. 8,598,219 (“the ’219 patent”). 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

9. 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.

10. 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.

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

12. This Court has personal jurisdiction over each of the Defendants by virtue of the fact that, *inter alia*, each Defendant has committed, aided, abetted, contributed to, and/or participated in the commission of a tortious act of patent infringement that has led to foreseeable harm and injury to Plaintiffs. This Court has personal jurisdiction over each of the Defendants for the additional reasons set forth above and below, and for other reasons that will be presented to the Court if such jurisdiction is challenged.

13. This Court has personal jurisdiction over Defendant Reddy Ltd.

14. This Court has personal jurisdiction over Defendant Reddy Inc.

15. This Court has personal jurisdiction over Defendant Sandoz.

16. This Court has personal jurisdiction over Defendant Teva USA.

17. This Court has personal jurisdiction over Defendant Teva Ltd.

THE PATENTS

18. On August 27, 2013, the '981 patent, titled "Liquid Pharmaceutical Formulations of Palonosetron," was duly and legally issued to Plaintiffs as assignees. A copy of the '981 patent is attached as Exhibit A.

19. On December 3, 2013, the '218 patent, titled "Liquid Pharmaceutical Formulations of Palonosetron," was duly and legally issued to Plaintiffs as assignees. A copy of the '218 patent is attached as Exhibit B.

20. On December 3, 2013, the '219 patent, titled "Liquid Pharmaceutical Formulations of Palonosetron," was duly and legally issued to Plaintiffs as assignees. A copy of the '219 patent is attached as Exhibit C.

21. Pursuant to 21 U.S.C. § 355(b)(1), the '981, '218, and '219 patents have been 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 '981 PATENT BY REDDY'S ANDA

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

23. Upon information and belief, Reddy submitted ANDA No. 201533 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA No. 201533 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 the '981 patent. ANDA No. 201533 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 '981 patent.

24. The '981 patent had not been issued at the time Reddy made its § 505(j)(2)(A)(vii)(IV) certification regarding certain of Plaintiffs' other Orange Book-listed patents.

25. Upon information and belief, Reddy has been aware of the existence of the '981 patent since at least as early as September 3, 2013, and is required by law to either amend its ANDA to contain a § 505(j)(2)(A)(vii)(IV) certification with respect to the '981 patent, or must relinquish its request that the FDA approve ANDA No. 201533 prior to the expiration of Plaintiffs' Orange Book-listed patents.

26. Reddy continues to seek approval of ANDA No. 201533 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 '981 patent.

27. By seeking approval of its ANDA 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 the '981 patent, Reddy has infringed that patent pursuant to 35 U.S.C. § 271(e)(2)(A).

28. Reddy Ltd. and Reddy Inc. are jointly and severally liable for any infringement of the '981 patent. This is because, upon information and belief, Reddy Ltd. and Reddy Inc. actively and knowingly caused to be submitted, assisted with, participated in, contributed to, and/or directed the submission of ANDA No. 201533 to the FDA.

29. Reddy's active and knowing participation in, contribution to, aiding, abetting, and/or inducement of the submission to the FDA of ANDA No. 201533 constitutes infringement of the '981 patent under 35 U.S.C. § 271(e)(2)(A).

30. Plaintiffs are entitled to a declaration that, if Reddy commercially manufactures, uses, offers for sale, 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, Reddy would infringe the '981 patent under 35 U.S.C. § 271(a), (b), and/or (c).

31. Plaintiffs will be irreparably harmed by Reddy'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 '218 PATENT BY REDDY'S ANDA

32. Plaintiffs reallege paragraphs 1-31 as if fully set forth herein.

33. Upon information and belief, Reddy submitted ANDA No. 201533 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA No. 201533 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 the '218 patent. ANDA No. 201533 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 '218 patent.

34. The '218 patent had not been issued at the time Reddy made its § 505(j)(2)(A)(vii)(IV) certification regarding certain of Plaintiffs' other Orange Book-listed patents.

35. Upon information and belief, Reddy is required by law to either amend its ANDA to contain a § 505(j)(2)(A)(vii)(IV) certification with respect to the '218 patent, or must relinquish its request that the FDA approve ANDA No. 201533 prior to the expiration of Plaintiffs' Orange Book-listed patents.

36. Reddy continues to seek approval of ANDA No. 201533 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 '218 patent.

37. By seeking approval of its ANDA 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 the '218 patent, Reddy has infringed that patent pursuant to 35 U.S.C. § 271(e)(2)(A).

38. Reddy Ltd. and Reddy Inc. are jointly and severally liable for any infringement of the '218 patent. This is because, upon information and belief, Reddy Ltd. and Reddy Inc. actively and knowingly caused to be submitted, assisted with, participated in, contributed to, and/or directed the submission of ANDA No. 201533 to the FDA.

39. Reddy's active and knowing participation in, contribution to, aiding, abetting, and/or inducement of the submission to the FDA of ANDA No. 201533 constitutes infringement of the '218 patent under 35 U.S.C. § 271(e)(2)(A).

40. Plaintiffs are entitled to a declaration that, if Reddy commercially manufactures, uses, offers for sale, 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, Reddy would infringe the '218 patent under 35 U.S.C. § 271(a), (b), and/or (c).

41. Plaintiffs will be irreparably harmed by Reddy'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 '219 PATENT BY REDDY'S ANDA

42. Plaintiffs reallege paragraphs 1-41 as if fully set forth herein.

43. Upon information and belief, Reddy submitted ANDA No. 201533 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA No. 201533 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 the '219 patent. ANDA No. 201533 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 '219 patent.

44. The '219 patent had not been issued at the time Reddy made its § 505(j)(2)(A)(vii)(IV) certification regarding certain of Plaintiffs' other Orange Book-listed patents.

45. Upon information and belief, Reddy is required by law to either amend its ANDA to contain a § 505(j)(2)(A)(vii)(IV) certification with respect to the '219 patent, or must relinquish its request that the FDA approve ANDA No. 201533 prior to the expiration of Plaintiffs' Orange Book-listed patents.

46. Reddy continues to seek approval of ANDA No. 201533 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 '219 patent.

47. By seeking approval of its ANDA 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 the '219 patent, Reddy has infringed that patent pursuant to 35 U.S.C. § 271(e)(2)(A).

48. Reddy Ltd. and Reddy Inc. are jointly and severally liable for any infringement of the '219 patent. This is because, upon information and belief, Reddy Ltd. and Reddy Inc. actively and knowingly caused to be submitted, assisted with, participated in, contributed to, and/or directed the submission of ANDA No. 201533 to the FDA.

49. Reddy's active and knowing participation in, contribution to, aiding, abetting, and/or inducement of the submission to the FDA of ANDA No. 201533 constitutes infringement of the '219 patent under 35 U.S.C. § 271(e)(2)(A).

50. Plaintiffs are entitled to a declaration that, if Reddy commercially manufactures, uses, offers for sale, 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, Reddy would infringe the '219 patent under 35 U.S.C. § 271(a), (b), and/or (c).

51. Plaintiffs will be irreparably harmed by Reddy'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 '981 PATENT
BY REDDY'S 505(b)(2) APPLICATION**

52. Plaintiffs reallege paragraphs 1-51 as if fully set forth herein.

53. Upon information and belief, Reddy submitted NDA No. 203050 to the FDA under § 505(b)(2) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(b)(2)). NDA No. 203050 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 the '981 patent. NDA No. 203050 specifically seeks FDA approval to market and sell generic versions 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 '981 patent.

54. The '981 patent had not issued at the time Reddy made its § 505(b)(2)(A)(iv) certification regarding certain of Plaintiffs' other Orange Book-listed patents.

55. Upon information and belief, Reddy has been aware of the existence of the '981 patent since at least as early as September 3, 2013, and is required by law to either amend its NDA to contain a § 505(b)(2)(A)(iv) certification with respect to the '981 patent, or must relinquish its request that the FDA approve NDA No. 203050 prior to the expiration of Plaintiffs' Orange Book-listed patents.

56. Reddy continues to seek approval of NDA No. 203050 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 '981 patent.

57. By seeking approval of its NDA 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 the '981 patent, Reddy has infringed that patent pursuant to 35 U.S.C. § 271(e)(2)(A).

58. Reddy Ltd. and Reddy Inc. are jointly and severally liable for any infringement of the '981 patent. This is because, upon information and belief, Reddy Ltd. and Reddy Inc. actively and knowingly caused to be submitted, assisted with, participated in, contributed to, and/or directed the submission of NDA No. 203050 to the FDA.

59. Reddy's active and knowing participation in, contribution to, aiding, abetting, and/or inducement of the submission to the FDA of NDA No. 203050 constitutes infringement of the '981 patent under 35 U.S.C. § 271(e)(2)(A).

60. Plaintiffs are entitled to a declaration that, if Reddy commercially manufactures, uses, offers for sale, 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, Reddy would infringe the '981 patent under 35 U.S.C. § 271(a), (b), and/or (c).

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

**COUNT V – INFRINGEMENT OF THE '218 PATENT
BY REDDY'S 505(b)(2) APPLICATION**

62. Plaintiffs reallege paragraphs 1-61 as if fully set forth herein.

63. Upon information and belief, Reddy submitted NDA No. 203050 to the FDA under § 505(b)(2) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(b)(2)). NDA No. 203050 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 the '218 patent. NDA No. 203050 specifically seeks FDA approval to market and sell generic versions 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 '218 patent.

64. The '218 patent had not issued at the time Reddy made its § 505(b)(2)(A)(iv) certification regarding certain of Plaintiffs' other Orange Book-listed patents.

65. Upon information and belief, Reddy is required by law to either amend its NDA to contain a § 505(b)(2)(A)(iv) certification with respect to the '218 patent, or must relinquish its request that the FDA approve NDA No. 203050 prior to the expiration of Plaintiffs' Orange Book-listed patents.

66. Reddy continues to seek approval of NDA No. 203050 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 '218 patent.

67. By seeking approval of its NDA 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 the '218 patent, Reddy has infringed that patent pursuant to 35 U.S.C. § 271(e)(2)(A).

68. Reddy Ltd. and Reddy Inc. are jointly and severally liable for any infringement of the '218 patent. This is because, upon information and belief, Reddy Ltd. and Reddy Inc. actively and knowingly caused to be submitted, assisted with, participated in, contributed to, and/or directed the submission of NDA No. 203050 to the FDA.

69. Reddy's active and knowing participation in, contribution to, aiding, abetting, and/or inducement of the submission to the FDA of NDA No. 203050 constitutes infringement of the '218 patent under 35 U.S.C. § 271(e)(2)(A).

70. Plaintiffs are entitled to a declaration that, if Reddy commercially manufactures, uses, offers for sale, 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, Reddy would infringe the '218 patent under 35 U.S.C. § 271(a), (b), and/or (c).

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

COUNT VI – INFRINGEMENT OF THE '981 PATENT BY SANDOZ'S ANDA

72. Plaintiffs reallege paragraphs 1-71 as if fully set forth herein.

73. Upon information and belief, Sandoz submitted ANDA No. 202521 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA No. 202521 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 the '981 patent. ANDA No. 202521 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 '981 patent.

74. The '981 patent had not been issued at the time Sandoz made its § 505(j)(2)(A)(vii)(IV) certification regarding certain of Plaintiffs' other Orange Book-listed patents.

75. Upon information and belief, Sandoz has been aware of the existence of the '981 patent since at least as early as September 3, 2013, and is required by law to either amend its ANDA to contain a § 505(j)(2)(A)(vii)(IV) certification with respect to the '981 patent, or must relinquish its request that the FDA approve ANDA No. 202521 prior to the expiration of Plaintiffs' Orange Book-listed patents.

76. Sandoz continues to seek approval of ANDA No. 202521 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 '981 patent.

77. By seeking approval of its ANDA 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 the '981 patent, Sandoz has infringed that patent pursuant to 35 U.S.C. § 271(e)(2)(A).

78. Sandoz's active and knowing participation in, contribution to, aiding, abetting, and/or inducement of the submission to the FDA of ANDA No. 202521 constitutes infringement of the '981 patent under 35 U.S.C. § 271(e)(2)(A).

79. Plaintiffs are entitled to a declaration that, if Sandoz commercially manufactures, uses, offers for sale, 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, Sandoz would infringe the '981 patent under 35 U.S.C. § 271(a), (b), and/or (c).

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

COUNT VII – INFRINGEMENT OF THE '218 PATENT BY SANDOZ'S ANDA

81. Plaintiffs reallege paragraphs 1-80 as if fully set forth herein.

82. Upon information and belief, Sandoz submitted ANDA No. 202521 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA No. 202521 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 the '218 patent. ANDA No. 202521 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 '218 patent.

83. The '218 patent had not been issued at the time Sandoz made its § 505(j)(2)(A)(vii)(IV) certification regarding certain of Plaintiffs' other Orange Book-listed patents.

84. Upon information and belief, Sandoz is required by law to either amend its ANDA to contain a § 505(j)(2)(A)(vii)(IV) certification with respect to the '218 patent, or must relinquish its request that the FDA approve ANDA No. 202521 prior to the expiration of Plaintiffs' Orange Book-listed patents.

85. Sandoz continues to seek approval of ANDA No. 202521 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 '218 patent.

86. By seeking approval of its ANDA 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 the '218 patent, Sandoz has infringed that patent pursuant to 35 U.S.C. § 271(e)(2)(A).

87. Sandoz's active and knowing participation in, contribution to, aiding, abetting, and/or inducement of the submission to the FDA of ANDA No. 202521 constitutes infringement of the '218 patent under 35 U.S.C. § 271(e)(2)(A).

88. Plaintiffs are entitled to a declaration that, if Sandoz commercially manufactures, uses, offers for sale, 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, Sandoz would infringe the '218 patent under 35 U.S.C. § 271(a), (b), and/or (c).

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

COUNT VIII – INFRINGEMENT OF THE '219 PATENT BY SANDOZ'S ANDA

90. Plaintiffs reallege paragraphs 1-89 as if fully set forth herein.

91. Upon information and belief, Sandoz submitted ANDA No. 202521 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA No. 202521 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 the '219 patent. ANDA No. 202521 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 '219 patent.

92. The '219 patent had not been issued at the time Sandoz made its § 505(j)(2)(A)(vii)(IV) certification regarding certain of Plaintiffs' other Orange Book-listed patents.

93. Upon information and belief, Sandoz is required by law to either amend its ANDA to contain a § 505(j)(2)(A)(vii)(IV) certification with respect to the '219 patent, or must relinquish its request that the FDA approve ANDA No. 202521 prior to the expiration of Plaintiffs' Orange Book-listed patents.

94. Sandoz continues to seek approval of ANDA No. 202521 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 '219 patent.

95. By seeking approval of its ANDA 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 the '219 patent, Sandoz has infringed that patent pursuant to 35 U.S.C. § 271(e)(2)(A).

96. Sandoz's active and knowing participation in, contribution to, aiding, abetting, and/or inducement of the submission to the FDA of ANDA No. 202521 constitutes infringement of the '219 patent under 35 U.S.C. § 271(e)(2)(A).

97. Plaintiffs are entitled to a declaration that, if Sandoz commercially manufactures, uses, offers for sale, 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, Sandoz would infringe the '219 patent under 35 U.S.C. § 271(a), (b), and/or (c).

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

COUNT IX – INFRINGEMENT OF THE '981 PATENT BY TEVA'S ANDA

99. Plaintiffs reallege paragraphs 1-98 as if fully set forth herein.

100. Upon information and belief, Teva submitted ANDA No. 090713 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA No. 090713 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 the '981 patent. ANDA No. 090713 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 '981 patent.

101. The '981 patent had not been issued at the time Teva made its § 505(j)(2)(A)(vii)(IV) certification regarding certain of Plaintiffs' other Orange Book-listed patents.

102. Upon information and belief, Teva has been aware of the existence of the '981 patent since at least as early as September 3, 2013, and is required by law to either amend its ANDA to contain a § 505(j)(2)(A)(vii)(IV) certification with respect to the '981 patent, or must relinquish its request that the FDA approve ANDA No. 090713 prior to the expiration of Plaintiffs' Orange Book-listed patents.

103. Teva continues to seek approval of ANDA No. 090713 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 '981 patent.

104. By seeking approval of its ANDA 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 the '981 patent, Teva has infringed that patent pursuant to 35 U.S.C. § 271(e)(2)(A).

105. Teva USA and Teva Ltd. are jointly and severally liable for any infringement of the '981 patent. This is because, upon information and belief, Teva USA and Teva Ltd. actively and knowingly caused to be submitted, assisted with, participated in, contributed to, and/or directed the submission of ANDA No. 090713 to the FDA.

106. Teva's active and knowing participation in, contribution to, aiding, abetting, and/or inducement of the submission to the FDA of ANDA No. 090713 constitutes infringement of the '981 patent under 35 U.S.C. § 271(e)(2)(A).

107. Plaintiffs are entitled to a declaration that, if Teva commercially manufactures, uses, offers for sale, 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, Teva would infringe the '981 patent under 35 U.S.C. § 271(a), (b), and/or (c).

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

COUNT X – INFRINGEMENT OF THE '218 PATENT BY TEVA'S ANDA

109. Plaintiffs reallege paragraphs 1-108 as if fully set forth herein.

110. Upon information and belief, Teva submitted ANDA No. 090713 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA No. 090713 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 the '218 patent. ANDA No. 090713 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 '218 patent.

111. The '218 patent had not been issued at the time Teva made its § 505(j)(2)(A)(vii)(IV) certification regarding certain of Plaintiffs' other Orange Book-listed patents.

112. Upon information and belief, Teva is required by law to either amend its ANDA to contain a § 505(j)(2)(A)(vii)(IV) certification with respect to the '218 patent, or must relinquish its request that the FDA approve ANDA No. 090713 prior to the expiration of Plaintiffs' Orange Book-listed patents.

113. Teva continues to seek approval of ANDA No. 090713 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 '218 patent.

114. By seeking approval of its ANDA 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 the '218 patent, Teva has infringed that patent pursuant to 35 U.S.C. § 271(e)(2)(A).

115. Teva USA and Teva Ltd. are jointly and severally liable for any infringement of the '218 patent. This is because, upon information and belief, Teva USA and Teva Ltd. actively and knowingly caused to be submitted, assisted with, participated in, contributed to, and/or directed the submission of ANDA No. 090713 to the FDA.

116. Teva's active and knowing participation in, contribution to, aiding, abetting, and/or inducement of the submission to the FDA of ANDA No. 090713 constitutes infringement of the '218 patent under 35 U.S.C. § 271(e)(2)(A).

117. Plaintiffs are entitled to a declaration that, if Teva commercially manufactures, uses, offers for sale, 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, Teva would infringe the '218 patent under 35 U.S.C. § 271(a), (b), and/or (c).

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

COUNT XI – INFRINGEMENT OF THE '219 PATENT BY TEVA'S ANDA

119. Plaintiffs reallege paragraphs 1-118 as if fully set forth herein.

120. Upon information and belief, Teva submitted ANDA No. 090713 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA No. 090713 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 the '219 patent. ANDA No. 090713 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 '219 patent.

121. The '219 patent had not been issued at the time Teva made its § 505(j)(2)(A)(vii)(IV) certification regarding certain of Plaintiffs' other Orange Book-listed patents.

122. Upon information and belief, Teva is required by law to either amend its ANDA to contain a § 505(j)(2)(A)(vii)(IV) certification with respect to the '219 patent, or must relinquish its request that the FDA approve ANDA No. 090713 prior to the expiration of Plaintiffs' Orange Book-listed patents.

123. Teva continues to seek approval of ANDA No. 090713 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 '219 patent.

124. By seeking approval of its ANDA 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 the '219 patent, Teva has infringed that patent pursuant to 35 U.S.C. § 271(e)(2)(A).

125. Teva USA and Teva Ltd. are jointly and severally liable for any infringement of the '219 patent. This is because, upon information and belief, Teva USA and Teva Ltd. actively and knowingly caused to be submitted, assisted with, participated in, contributed to, and/or directed the submission of ANDA No. 090713 to the FDA.

126. Teva's active and knowing participation in, contribution to, aiding, abetting, and/or inducement of the submission to the FDA of ANDA No. 090713 constitutes infringement of the '219 patent under 35 U.S.C. § 271(e)(2)(A).

127. Plaintiffs are entitled to a declaration that, if Teva commercially manufactures, uses, offers for sale, 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, Teva would infringe the '219 patent under 35 U.S.C. § 271(a), (b), and/or (c).

128. Plaintiffs will be irreparably harmed by Teva'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 Defendants Reddy Ltd., Reddy Inc., Sandoz, Teva USA, and Teva Ltd. have infringed the '981, '218, and '219 patents by submitting the aforesaid ANDAs;

B. A Judgment be entered declaring that Defendants Reddy Ltd. and Reddy Inc. have infringed the '981 and '218 patents by submitting the aforesaid NDA;

C. An Order be issued pursuant to 35 U.S.C. § 271(e)(4)(A) that the effective date of any approval of any of Defendants' ANDAs identified in this Complaint be a date that is

not earlier than the expiration date of the '981, '218, and '219 patents, or any later expiration of exclusivity for the '981, '218, and '219 patents to which Plaintiffs are or become entitled;

D. An Order be issued pursuant to 35 U.S.C. § 271(e)(4)(A) that the effective date of any approval of Defendants Reddy Ltd. and Reddy Inc.'s NDA identified in this Complaint be a date that is not earlier than the expiration date of the '981 and '218 patents, or any later expiration of exclusivity for the '981 and '218 patents to which Plaintiffs are or become entitled;

E. An Order be issued that Defendants Reddy Ltd., Reddy Inc., Sandoz, Teva USA, and Teva Ltd., their officers, agents, servants and employees, and those persons in active concert or participation with any of them, are preliminarily and permanently enjoined from commercially manufacturing, using, offering for sale, importing, or selling 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 '981, '218, and '219 patents, prior to the expiration of the '981, '218, and '219 patents, including any extensions to which Plaintiffs are or become entitled; and

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

Dated: December 27, 2013

Respectfully submitted,

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EXHIBIT A



US008518981B2

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

(10) **Patent No.:** **US 8,518,981 B2**
(45) **Date of Patent:** ***Aug. 27, 2013**

(54) **LIQUID PHARMACEUTICAL FORMULATIONS OF PALONOSETRON**
(75) Inventors: **Giorgio Calderari, Rancate (CH); Daniele Bonadeo, Varese (IT); Roberta Cannella, Varese (IT); Andrew Miksztal, Palo Alto, CA (US); Thomas Malefy, Carmel Valley, CA (US); Kathleen Lee, Palo Alto, CA (US)**

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(73) Assignees: **Helsinn Healthcare SA, Lugano/Pazzallo (CH); Roche Palo Alto LLC, Palo Alto, CA (US)**

FOREIGN PATENT DOCUMENTS

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

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This patent is subject to a terminal disclaimer.

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(21) Appl. No.: **13/087,012**

Opposition 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).

(22) Filed: **Apr. 14, 2011**

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 Get al., Proc. Am. Soc. Clin. Oncol 2002 21 Abs 449 (2002).

(65) **Prior Publication Data**

US 2011/0192493 A1 Aug. 11, 2011

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.

Related U.S. Application Data

(63) 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.

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.

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

(51) **Int. Cl.**
A01N 43/52 (2006.01)

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.

(52) **U.S. Cl.**
USPC **514/397**

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

(58) **Field of Classification Search**
USPC **514/397**
See application file for complete search history.

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(Continued)

Primary Examiner — Shirley V Gembeh

(74) *Attorney, Agent, or Firm* — Arnall Golden Gregory LLP; Clark G. Sullivan; Kimberly Bond

(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.

12 Claims, No Drawings

(56)

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**LIQUID PHARMACEUTICAL
 FORMULATIONS OF PALONOSETRON**

The present application is a continuation of U.S. Ser. No. 11/186,311 filed Jul. 21, 2005 (allowed), 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-HT₃ (5-hydroxytryptamine) receptor antagonists has been developed that treat such emesis by antagonizing cerebral functions associated with the 5-HT₃ receptor. See *Drugs Acting on 5-Hydroxytryptamine Receptors*: The Lancet Sep. 23, 1989 and references cited therein. Drugs within this class include ondansetron, granisetron, alosetron, tropisetron, and dolasetron. These 5-HT₃ antagonists are often administered intravenously shortly before chemotherapy or radiotherapy is initiated, and can be administered more than once during a cycle of chemotherapy or radiotherapy. In addition, they are often supplied as tablets or oral elixirs to either supplement an intravenous administration, or to ease home usage of the drug if the patient is self-administering the chemotherapeutic regimen.

Because some chemotherapeutic agents can induce emesis over extended periods of several days even when they are administered only once, it would be desirable to administer an emesis-inhibiting drug such as a 5-HT₃ antagonist every day until the risk of emesis has substantially subsided. The present class of 5-HT₃ antagonists has not proven especially helpful meeting this need, however, because the 5-HT₃ receptor antagonists currently marketed have proven to be less effective in controlling delayed nausea and vomiting than they are at controlling acute emesis. Sabra, K, *Choice of a 5HT₃ Receptor Antagonist for the Hospital Formulary*. EHP, October 1996; 2 (suppl 1):S19-24.

Recently, clinical investigations have been made concerning palonosetron, a new 5-HT₃ 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-HT₃ 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

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 -continued

Ingredient	Mg
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® (Nortaris) 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-HT₃ 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

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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 $\frac{1}{10}^{\text{th}}$ the amount of other previously known compounds for treating emesis, which surprisingly allows the use of concentrations of palonosetron far below those that would ordinarily be expected. Thus, in one embodiment the invention provides a pharmaceutically stable solution for preventing or reducing emesis comprising a) from about 0.01 mg/mL to about 5 mg/mL palonosetron or a pharmaceutically acceptable salt thereof; and b) a pharmaceutically acceptable carrier.

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

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

DETAILED DESCRIPTION OF THE INVENTION

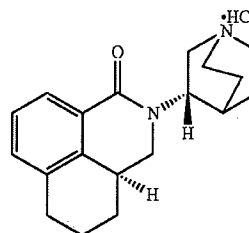
Definitions

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

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

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

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

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

"Pharmaceutically acceptable salts" means salts which are pharmaceutically acceptable, as defined above, and which possess the desired pharmacological activity. Such salts include acid addition salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or with organic acids such as acetic acid, propionic acid, hexanoic acid, heptanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, o-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedithionylsulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid p-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, p-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, 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 $\frac{1}{10}^{\text{th}}$ 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 embodi-

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ments, 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

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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 e) 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

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containers (preferably 5 ml. vials); h) 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

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-continued

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

*calculated as a free base

Example 5

Formulation II

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

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

*calculated as a free base

Example 6

Stability of Palonosetron without Dexamethasone

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

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

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

Example 7

Stability of Palonosetron with Dexamethasone

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

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 method of manufacturing and terminally sterilizing a finished single unit dose vial of palonosetron or a pharmaceutically acceptable salt thereof comprising: a) providing one or more sterile open containers; b) filling said containers with a pharmaceutically stable solution of palonosetron or a phar-

maceutically acceptable salt thereof; c) sealing said filled containers; d) terminally sterilizing said sealed, filled containers; and e) optionally adjusting the pH of said solution using HCl or NaOH prior to step (c), wherein the pharmaceutically stable solution has a pH of from about 4.0 to about 6.0 and comprises palonosetron hydrochloride in a concentration of from about 0.03 mg/mL to about 0.2 mg/mL based on the weight of the free base, an aqueous carrier, and a tonicity agent, and wherein the pharmaceutically stable solution optionally comprises one or a combination of mannitol, a chelating agent, and a citrate buffer.

2. The method of claim 1, wherein said solution comprises 0.05 mg/ml of palonosetron hydrochloride based on the weight of the free base.

3. The method of claim 1, wherein said solution comprises HCl or NaOH as a pH adjusting agent.

4. The method of claim 1, wherein said solution has a pH of from 4.5 to 5.5, HCl or NaOH as a pH adjusting agent, and mannitol.

5. A single unit dose of palonosetron hydrochloride made by the method of claim 4.

6. The method of claim 1, wherein said solution has a pH of from 4.5 to 5.5, HCl or NaOH as a pH adjusting agent, a chelating agent and mannitol.

7. A single unit dose of palonosetron hydrochloric made by the method of claim 6.

8. The method of claim 1, wherein said solution comprises HCl or NaOH as a pH adjusting agent, a chelating agent and mannitol.

9. The method of claim 1, wherein said solution comprises a chelating agent and mannitol.

10. The method of claim 1, wherein said solution comprises a chelating agent.

11. The method of claim 1, wherein said solution comprises mannitol.

12. A single unit dose of palonosetron hydrochloride made by the method of claim 1.

* * * * *

EXHIBIT B



US008598218B2

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

(10) **Patent No.:** **US 8,598,218 B2**
(45) **Date of Patent:** ***Dec. 3, 2013**

- (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

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

(51) **Int. Cl.**
A01N 43/52 (2006.01)

(52) **U.S. Cl.**
USPC **514/397**

(58) **Field of Classification Search**
USPC **514/397**
See application file for complete search history.

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(57) **ABSTRACT**

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

11 Claims, No Drawings

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LIQUID PHARMACEUTICAL FORMULATIONS OF PALONOSETRON

The present application is a continuation of U.S. Ser. No. 11/186,311 filed Jul. 21, 2005 (allowed), 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-HT₃ (5-hydroxytryptamine) receptor antagonists has been developed that treat such emesis by antagonizing cerebral functions associated with the 5-HT₃ receptor. See *Drugs Acting on 5-Hydroxytryptamine Receptors*: The Lancet Sep. 23, 1989 and references cited therein. Drugs within this class include ondansetron, granisetron, alosetron, tropisetron, and dolasetron. These 5-HT₃ antagonists are often administered intravenously shortly before chemotherapy or radiotherapy is initiated, and can be administered more than once during a cycle of chemotherapy or radiotherapy. In addition, they are often supplied as tablets or oral elixirs to either supplement an intravenous administration, or to ease home usage of the drug if the patient is self-administering the chemotherapeutic regimen.

Because some chemotherapeutic agents can induce emesis over extended periods of several days even when they are administered only once, it would be desirable to administer an emesis-inhibiting drug such as a 5-HT₃ antagonist every day until the risk of emesis has substantially subsided. The present class of 5-HT₃ antagonists has not proven especially helpful meeting this need, however, because the 5-HT₃ receptor antagonists currently marketed have proven to be less effective in controlling delayed nausea and vomiting than they are at controlling acute emesis. Sabra, K, *Choice of a 5HT₃ Receptor Antagonist for the Hospital Formulary*. EHP, October 1996; 2 (suppl 1):S19-24.

Recently, clinical investigations have been made concerning palonosetron, a new 5-HT₃ 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-HT₃ 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

-continued

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

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

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

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

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

SUMMARY OF THE INVENTION

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

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

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

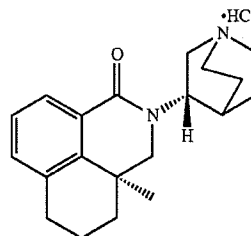
Definitions

"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 mL).

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

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

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

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

"Pharmaceutically acceptable salts" means salts which are pharmaceutically acceptable, as defined above, and which possess the desired pharmacological activity. Such salts include acid addition salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or with organic acids such as acetic acid, propionic acid, hexanoic acid, heptanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, o-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedithionylsulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid p-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, p-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, 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 $1/10^{\text{th}}$ 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 embodi-

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ments, 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

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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 e) 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

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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

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-continued

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

*calculated as a free base

Example 5

Formulation II

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

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

*calculated as a free base

Example 6

Stability of Palonosetron without Dexamethasone

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

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

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

Example 7

Stability of Palonosetron with Dexamethasone

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

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 method of manufacturing and terminally sterilizing a finished single unit dose vial of palonosetron or a pharmaceutically acceptable salt thereof comprising:

- a) providing one or more sterile open containers;
- b) filling said containers with about 5 ml of an aqueous pharmaceutically stable solution of palonosetron or a pharmaceutically acceptable salt thereof;
- c) sealing said filled containers;
- d) terminally sterilizing said sealed, filled containers; and
- e) optionally adjusting said solution to a pH of from about 4.0 to about 6.0 prior to step (c),

wherein the pharmaceutically stable solution comprises palonosetron hydrochloride in an amount of about 0.25

mg based on the weight of its free base, an aqueous carrier, and a tonicity agent, and wherein the pharmaceutically stable solution optionally comprises one or a combination of mannitol, a chelating agent, and a citrate buffer.

2. The method of claim 1, wherein said solution comprises a pH adjusting agent.

3. The method of claim 1, wherein said solution has a pH of from 4.5 to 5.5, and wherein said solution further comprises mannitol.

4. A finished single unit dose vial of palonosetron or a pharmaceutically acceptable salt thereof manufactured by the method of claim 3.

5. The method of claim 1, wherein said solution further comprises a pH adjusting agent, a chelating agent, and mannitol.

6. The method of claim 1, wherein said solution comprises HCl or NaOH as a pH adjusting agent, a chelating agent, and mannitol.

7. The method of claim 1, wherein said solution comprises a chelating agent and mannitol.

8. The method of claim 1, wherein said solution comprises a chelating agent.

9. The method of claim 1, wherein said solution comprises mannitol.

10. A finished single unit dose vial of palonosetron or a pharmaceutically acceptable salt thereof manufactured by the method of claim 1.

11. A method of manufacturing and terminally sterilizing a finished single unit dose vial of palonosetron or a pharmaceutically acceptable salt thereof comprising:

- a) providing one or more sterile open containers;
- b) filling said containers with an aqueous pharmaceutically stable solution of palonosetron or a pharmaceutically acceptable salt thereof having a palonosetron concentration of 0.05 mg/mL based on the weight of its free base;
- c) sealing said filled containers;
- d) terminally sterilizing said sealed, filled containers; and
- e) optionally adjusting said solution to a pH of from about 4.0 to about 6.0 prior to step (c),

wherein the pharmaceutically stable solution comprises palonosetron hydrochloride in a concentration of 0.05 mg/mL based on the weight of its free base, an aqueous carrier, and a tonicity agent, and

wherein the pharmaceutically stable solution optionally comprises one or a combination of mannitol, a chelating agent, and a citrate buffer.

* * * * *

EXHIBIT C



US008598219B2

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

(10) **Patent No.:** **US 8,598,219 B2**
(45) **Date of Patent:** ***Dec. 3, 2013**

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

(51) **Int. Cl.**
A01N 43/52 (2006.01)

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USPC **514/397**

(58) **Field of Classification Search**
USPC **514/397**
See application file for complete search history.

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(57) **ABSTRACT**

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

8 Claims, No Drawings

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**LIQUID PHARMACEUTICAL
FORMULATIONS OF PALONOSETRON**

FIELD OF THE INVENTION

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

BACKGROUND OF THE INVENTION

Emesis is a devastating consequence of cytotoxic therapy, radiotherapy, and post-operative environments that drastically affects the quality of life of people undergoing such treatments. In recent years a class of drugs referred to as 5-HT₃ (5-hydroxytryptamine) receptor antagonists has been developed that treat such emesis by antagonizing cerebral functions associated with the 5-HT₃ receptor. See *Drugs Acting on 5-Hydroxytryptamine Receptors*: The Lancet Sep. 23, 1989 and references cited therein. Drugs within this class include ondansetron, granisetron, alosetron, tropisetron, and dolasetron. These 5-HT₃ antagonists are often administered intravenously shortly before chemotherapy or radiotherapy is initiated, and can be administered more than once during a cycle of chemotherapy or radiotherapy. In addition, they are often supplied as tablets or oral elixirs to either supplement an intravenous administration, or to ease home usage of the drug if the patient is self-administering the chemotherapeutic regimen.

Because some chemotherapeutic agents can induce emesis over extended periods of several days even when they are administered only once, it would be desirable to administer an emesis-inhibiting drug such as a 5-HT₃ antagonist every day until the risk of emesis has substantially subsided. The present class of 5-HT₃ antagonists has not proven especially helpful meeting this need, however, because the 5-HT₃ receptor antagonists currently marketed have proven to be less effective in controlling delayed nausea and vomiting than they are at controlling acute emesis. Sabra, K, *Choice of a 5HT₃ Receptor Antagonist for the Hospital Formulary*. EHP, October 1996; 2 (suppl 1):S19-24.

Recently, clinical investigations have been made concerning palonosetron, a new 5-HT₃ 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-HT₃ 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.

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

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

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

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

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

Therefore, there exists a need for a palonosetron formulation with increased stability and thereby increased shelf life. There also exists a need for an appropriate range of concentrations for both the 5-HT₃ 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 1/10th 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

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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.

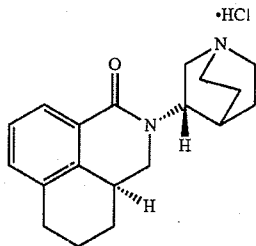
DETAILED DESCRIPTION OF THE INVENTION

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

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weight of the free base. Concentrations of all other ingredients are given based on the weight of ingredient added to the solution.

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

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

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

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

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

Example 7

Stability of Palonosetron with Dexamethasone

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

Test samples of palonosetron HCl 5 µg/mL with dexamethasone (as sodium phosphate) 0.2 mg/mL and also 0.4 mg/mL were prepared in polyvinyl chloride (PVC) minibags of each infusion solution. Additionally, palonosetron HCl 25 µg/mL with dexamethasone (as sodium phosphate) 0.33 mg/mL in each infusion solution were prepared as 10 mL of test solution in 20-mL polypropylene syringes. Evaluations for physical and chemical stability were performed on samples taken initially and after 1, 3, 7, and 14 days of storage at 4° C. and after 1, 4, 24, and 48 hours at 23° C. Physical stability was assessed using visual observation in normal

room light and using a high-intensity monodirectional light beam. In addition, turbidity and particle content were measured electronically. Chemical stability of the drug was evaluated by using a stability-indicating high performance liquid chromatographic (HPLC) analytical technique.

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

Example 8

Formulation III

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

Ingredient	Amount (mg)
Palonosetron Hydrochloride	0.75 ^{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 isotonic solution, said solution comprising:
 palonosetron hydrochloride in an amount of 0.25 mg based on the weight of its free base;
 from 0.005 mg/mL to 1.0 mg/mL EDTA; and
 from 10 mg/mL to 80 mg/mL mannitol,
 wherein said formulation is stable at 24 months when stored at room temperature.
2. The pharmaceutical formulation of claim 1, wherein said EDTA is in an amount of 0.5 mg/mL.
3. The pharmaceutical formulation of claim 1, wherein said mannitol is in an amount of 41.5 mg/mL.
4. The pharmaceutical formulation of claim 1, wherein said solution further comprises a citrate buffer.
5. The pharmaceutical formulation of claim 4, wherein said citrate buffer is at a concentration of 20 millimolar.
6. The pharmaceutical formulation of claim 1, wherein said solution is buffered at a pH of 5.0 ± 0.5.
7. The pharmaceutical formulation of claim 1, wherein said EDTA is in an amount of 0.5 mg/mL, wherein said mannitol is in an amount of 41.5 mg/mL, wherein said solution further comprises a citrate buffer at a concentration of 20 millimolar, and wherein said solution is buffered at a pH of 5.0 ± 0.5.
8. 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 isotonic solution, said solution comprising:
 palonosetron hydrochloride in an amount of 0.25 mg based on the weight of its free base;
 from 0.005 mg/mL to 1.0 mg/mL EDTA; and
 from 10 mg/mL to 80 mg/mL mannitol, wherein said formulation is stable at 18 months when stored at room temperature.

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