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**Calderari et al.**

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(45) **Date of Patent:** **\*Jun. 14, 2011**

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

(75) Inventors: **Giorgio Calderari**, Rancate (CH); **Daniele Bonadeo**, Varese (IT); **Roberta Cannella**, Varese (IT); **Enrico Braglia**, Pazzallo (CH); **Riccardo Braglia**, Pazzallo (CH); **Andrew Miksztal**, Palo Alto, CA (US); **Thomas Malefyt**, Carmel Valley, CA (US); **Kathleen M. Lee**, Palo Alto, CA (US)

(73) Assignees: **Helsinn Healthcare S.A.**, Lugano (CH); **Roche Palo Alto LLC**, Palo Alto, CA (US)

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

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(21) Appl. No.: **11/388,270**

(22) Filed: **Mar. 24, 2006**

(65) **Prior Publication Data**

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**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.

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

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

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

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

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,695,578 A	9/1987	Coates et al.	514/397
4,753,789 A	6/1988	Tyers et al.	424/10
4,886,808 A	12/1989	King	514/299
4,906,755 A	3/1990	Gittos	546/94
4,929,632 A	5/1990	Tyers et al.	514/397
4,937,247 A	6/1990	King	514/299
5,011,846 A	4/1991	Gittos et al.	514/294
5,034,398 A	7/1991	King	514/299
5,202,333 A	4/1993	Berger et al.	514/296
5,240,954 A	8/1993	Tyers et al.	514/395
5,272,137 A	12/1993	Blase et al.	
5,344,658 A	9/1994	Collin	424/489
5,578,628 A	11/1996	Tyers et al.	514/397
5,578,632 A	11/1996	Tyers et al.	514/397
5,622,720 A	4/1997	Collin	424/489
5,854,270 A	12/1998	Gambhir	
5,922,749 A	7/1999	Tyers et al.	514/397

6,284,749 B1 *	9/2001	Castillo et al.	514/159
6,287,592 B1	9/2001	Dickinson	
6,294,548 B1	9/2001	James	514/299
2001/0020029 A1	9/2001	James	514/299
2003/0095926 A1	5/2003	Dugger, III	424/43

FOREIGN PATENT DOCUMENTS

WO	WO 03/100091 A	12/2003
WO	WO-2004045615 A1 *	6/2004
WO	W02004067005	8/2004
WO	WO-2004073714 A1 *	9/2004

OTHER PUBLICATIONS

Matsumoto et al., "Yakuzaijaku Manual", 1st edition, Nanzando Co., Ltd. (1989) 2 pages.\*

Barton (Citrate Buffer Calculation, 2000, 2pgs.\*

Eglen, R. M. et al., Pharmacological Characterization of RS 25259-197, a Novel and Selective 5-HT<sub>3</sub> Receptor Antagonist, in vivo, extracted from *British Journal of Pharmacology*, 1995, vol. 114, No. 4, pp. 860-866.

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

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

Gaster, Laramie M. and King, Frank D., Serotonin 5-HT<sub>3</sub> and 5-HT<sub>4</sub> Receptor Antagonists, extracted from *Medicinal Research Reviews*, 1997, vol. 17, No. 2, pp. 163-214.

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

Tang, Jun et al., The Efficacy of RS-25259, a Long-Acting Selective 5-HT<sub>3</sub> Receptor Antagonist, for Preventing Postoperative Nausea and Vomiting After Hysterectomy Procedures, extracted from *Anesthesia and Analgesia*, 1998, vol. 87, pp. 462-467.

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

Piraccini, Gaia et al., An Interesting 5-HT<sub>3</sub> Receptor Antagonist Antiemetic for Patients Undergoing Chemotherapy-Based Conditioning Regimens?, extracted from *Blood*, Nov. 16, 2001, vol. 98, No. 11, part 2, p. 350b, abstract No. 5169.

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

(Continued)

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(57) **ABSTRACT**

The present invention relates to shelf-stable liquid formulations of palonosetron for reducing chemotherapy and radiotherapy induced emesis with palonosetron. The formulations are particularly

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4,695,578 A	9/1987	Coates et al.	514/397
4,753,789 A	6/1988	Tyers et al.	424/10
4,886,808 A	12/1989	King	514/299
4,906,755 A	3/1990	Gittos	546/94
4,929,632 A	5/1990	Tyers et al.	514/397
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5,011,846 A	4/1991	Gittos et al.	514/294
5,034,398 A	7/1991	King	514/299
5,202,333 A	4/1993	Berger et al.	514/296
5,240,954 A	8/1993	Tyers et al.	514/395
5,272,137 A	12/1993	Blase et al.	
5,344,658 A	9/1994	Collin	424/489
5,578,628 A	11/1996	Tyers et al.	514/397
5,578,632 A	11/1996	Tyers et al.	514/397
5,622,720 A	4/1997	Collin	424/489
5,854,270 A	12/1998	Gambhir	
5,922,749 A	7/1999	Tyers et al.	514/397
5,955,488 A	9/1999	Winterborn	514/399
6,063,802 A	5/2000	Winterborn	514/397

6,284,749 B1 *	9/2001	Castillo et al.	514/159
6,287,592 B1	9/2001	Dickinson	
6,294,548 B1	9/2001	James	514/299
2001/0020029 A1	9/2001	James	514/299
2003/0095926 A1	5/2003	Dugger, III	424/43

**FOREIGN PATENT DOCUMENTS**

WO	WO 03/100091 A	12/2003
WO	WO-2004045615 A1 *	6/2004
WO	W02004067005	8/2004
WO	WO-2004073714 A1 *	9/2004

**OTHER PUBLICATIONS**

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

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Gaster, Laramie M. and King, Frank D., Serotonin 5-HT<sub>3</sub> and 5-HT<sub>4</sub> Receptor Antagonists, extracted from *Medicinal Research Reviews*, 1997, vol. 17, No. 2, pp. 163-214.

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

Tang, Jun et al., The Efficacy of RS-25259, a Long-Acting Selective 5-HT<sub>3</sub> Receptor Antagonist, for Preventing Postoperative Nausea and Vomiting After Hysterectomy Procedures, extracted from *Anesthesia and Analgesia*, 1998, vol. 87, pp. 462-467.

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

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

(57) **ABSTRACT**

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

**6 Claims, No Drawings**

## OTHER PUBLICATIONS

- Navari, Rudolph M., Pathogenesis-Based Treatment of Chemotherapy-Induced Nausea and Vomiting—Two New Agents, extracted from *Journal of Supportive Oncology*, 2003, vol. 1(2), pp. 89-103.
- Michael J. Pikal, "Freeze Drying", *Encyclopedia of Pharmaceutical Technology*, Third Edition, Jan. 2007, pp. 1824-1825, vol. 3, Informa Pharmaceuticals & Healthcare.
- 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).
- Palonosetron: a phase II dose ranging study to assess over a 7 day period the single dose pharmacokinetic profile of palonosetron in patients receiving highly emetogenic chemotherapy. Piraccini G et al., *Proc. Am. Soc. Clin. Oncol* 2002 21 Abs 449 (2002).
- Formulation and administration techniques to minimize injection pain and tissue damage associated with parenteral products. Larry A. Gatlin; Carol A. Brister Gatlin, [from *Injectable Drug Development: Techniques to Reduce Pain and Irritation* [Edited by Pramod K. Gupta, Gayle A. Brazeau; Published by Informa Health Care (original copyright of 1999 by Interpharma Press), 1999; ISBN 1574910957, 9781574910957], p. 401-421.
- Parenteral Dosage Forms. Joanne Broadhead. [from Part 11—Early drug development, *Pharmaceutical preformulation and formulation: a practice guide from candidate drug selection to commercial dosage form* [Edited by Mark Gibson; Published by Interpharma Press, 2001; ISBN 1574911201, 9781574911206], p. 331-353.
- Opposition Brief filed by Tecnimed Sociedade Tecnico-Medicinal S.A., opposition to European Patent No. 1601359 B1, Jul. 8, 2009.
- Response brief filed by Helsinn Healthcare S.A. dated Jul. 13, 2007, in response to the communication pursuant to Art. 96(2) EPC of Jan. 3, 2007 regarding Serial No. 04 706 657.6-2123.
- European Patent Office official communication dated Jul. 19, 2006 regarding Serial No. 04 706 657.6.
- Response of Helsinn Healthcare S.A. dated Nov. 29, 2006 regarding EPO official communication dated Jul. 19, 2006.
- Lachman et al., *The Theory and Practice of Industrial Pharmacy*, 1986, third edition, pp. 652-784.
- Summary of Product Characteristics for Aloxi 250.
- Declaration of Valentino J. Stella, Ph.D.
- Opposition Brief filed by Martin Paul White, opposition to European Patent No. 1601359 B1, Jul. 8, 2009.
- Wong et al. (1995), in *British Journal of Pharmacology*, vol. 114, pp. 851-859 and Eglen et al. (1995), in *British Journal of Pharmacology*, vol. 114, pp. 860-866.
- Cover page and pp. 642-644 and 783-784 of *The Theory and Practice of Industrial Pharmacy*, Third Edition, Lea and Febiger (1986).
- Cover page and pp. 514-515 of *Modern Pharmaceutics*, Second Edition, Marcel Dekker (1990).
- Cover page and pp. 142-143 of *Pharmaceutical Dosage Forms: Parenteral Medications* vol. 1, Second Edition, Marcel Dekker (1992).
- Scientific Discussion from the European Public Assessment Report for Aloxi (Palonosetron Hydrochloride).
- Kranke et al. 2007, "Recent advances, trends and economic considerations in . . ." *Expert Opinion Pharmacother.*, 8 (18): 3217-3235.
- Morrow et al. 1995, Progress in reducing nausea and emesis. Comparisons of ondansetron, granisetron, and tropisetron. *Cancer*, vol. 76 No. 3 pp. 343-357.
- Daniele Bonadeo, "Supplemental Declaration of Daniele Bonadeo 37 C.F.R. 1.132", U.S. Appl. No. 11/388,270, Jun. 8, 2009.
- Chaitow, 1990, 3 pages.
- USPTO Office Action, U.S. Appl. No. 11/388,268, Filing Date Mar. 24, 2006, Mail Date Mar. 29, 2010.
- USPTO Office Action, U.S. Appl. No. 11/129,839, Mail Date Jan. 15, 2010.
- Israilli, Zafar II., *Clinical Pharmacology of Serotonin Receptor Type-3 (5-HT<sub>3</sub>) Antagonists*, *Curr. Med. Chem.—Central Nervous System Agents*, 2001, 1, 171-199.
- USPTO Office Action, U.S. Appl. No. 11/201,035, Mail Date Aug. 19, 2009.
- Response of Helsinn Healthcare to opposition of EP Serial No. 04 706 657.6 dated Feb. 11, 2010.
- Annex 1 (Statement of Waldo Mossi, Ph.D.) to Response of Helsinn Healthcare to opposition of EP Serial No. 04 706 657.6 dated Feb. 11, 2010.
- Annex 2 to Response of Helsinn Healthcare to opposition of EP Serial No. 04 706 657.6 dated Feb. 11, 2010.
- Annex 3 to Response of Helsinn Healthcare to opposition of EP Serial No. 04 706 657.6 dated Feb. 11, 2010.
- 6<sup>th</sup> Edition, *Handbook of Pharmaceutical Excipients* (2009), pp. 247-250n (RPS Publishing).

\* cited by examiner

**LIQUID PHARMACEUTICAL FORMULATIONS OF PALONOSETRON**

The present invention claims priority to PCT/EP04/000888, filed Jan. 30, 2004, which claims priority to U.S. Provisional Patent Application No. 60/444,351, filed Jan. 30, 2003. The present application is also a continuation of currently pending U.S. patent application Ser. No. 11/186,311, filed Jul. 21, 2005. The content of these applications is incorporated herein by reference.

**BACKGROUND OF THE INVENTION**

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

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

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

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

Ingredient	Mg
Palonosetron HCl	10-100 mg.
Dextrose Monohydrate	q.s. to make isotonic
Citric Acid Monohydrate	1.05 mg.

-continued

Ingredient	Mg
Sodium Hydroxide	0.18 mg.
WFJ	To 1.0 ml.

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

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

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

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

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

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

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

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

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

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

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

**SUMMARY OF THE INVENTION**

The inventors have made a series of discoveries that support a surprisingly effective and versatile formulation for the treatment and prevention of emesis using palonosetron. 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  $\frac{1}{10}^{th}$  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/l 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

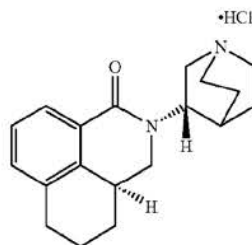
### Definitions

"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, p-filled syringes. Vial also means a sealed container of medication that is used one time only, and includes breakable and non-breakable 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 suture:

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

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

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

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

### Discussion

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

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