

# LIQUID PHARMACEUTICAL FORMULATIONS OF PALONOSETRON

## FIELD OF THE INVENTION

5 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

10 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.*  
15 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  
20 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  
25 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, Oct. 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. Patent 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  
5 reduce delayed-onset nausea induced by chemotherapeutic agents. However, formulating palonosetron in liquid formulations has not proven an easy task, typically due to shelf-stability issues. U.S. Pat. No. 5,202,333 discloses an intravenous formulation of palonosetron in example 13 that contains the following ingredients:

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

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

Ondansetron, its uses, and medicaments made with ondansetron are disclosed in U.S. Patent Numbers 4,695,578, 4,753,789, 4,929,632, 5,240,954, 5,344,658, 5,578,628,  
15 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  
20 Disintegrating Tablets.

Granisetron, its uses, and medicaments made with granisetron are disclosed in U.S. Patent Numbers 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.

5 Alosetron, its uses, and medicaments made with alosetron are disclosed in U.S. Patent Numbers 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.

10 Dolasetron, its uses, and medicaments made with ondansetron are disclosed in U.S. Patent Numbers 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.

15 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.

20 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.

25 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 18 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**

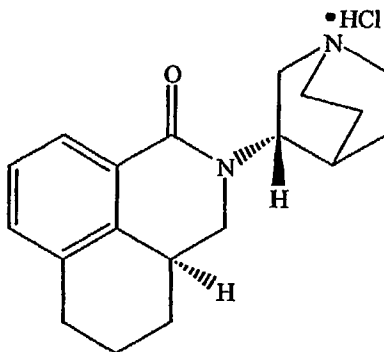
5        DEFINITIONS

“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, 10 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 15 any other element, integer or step, or group of elements, integers or steps

“Palonosetron” means (3a*S*)-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-1*H*benz[*de*]isoquinoline, and is preferably present as the monohydrochloride. Palonosetron monohydrochloride can be represented by the following chemical structure:

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Concentrations -- When concentrations of palonosetron are given herein, the concentration is measured in terms of the weight of the free base. Concentrations of all

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