

UNITED PATENT NON-PROVISIONAL PATENT APPLICATION
FOR
LIQUID PHARMACEUTICAL FORMULATIONS OF PALONOSETRON

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5579776v1

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

v.

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
5 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
10 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
15 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
20 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
25 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

5579776v1 2

acute emesis. Sabra, K, *Choice of a 5HT₃ 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-HT₃ 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-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. Patent Numbers 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

5579776v1 3

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.

5 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.

10 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.

15 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.

20 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.

25 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.

5579776v1 4

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
5 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
10 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
15 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)
20 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
25 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

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