Title: LIQUID PHARMACEUTICAL FORMULATIONS OF PALONOSETRON

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.
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, 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:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palonosetron HCl</td>
<td>10-100 mg.</td>
</tr>
<tr>
<td>Dextrose Monohydrate</td>
<td>q.s. to make Isotonic</td>
</tr>
<tr>
<td>Citric Acid Monohydrate</td>
<td>1.05 mg.</td>
</tr>
<tr>
<td>Sodium Hydroxide</td>
<td>0.18 mg.</td>
</tr>
<tr>
<td>WFI</td>
<td>To 1.0 ml.</td>
</tr>
</tbody>
</table>

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 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. 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.

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.

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.

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 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 \((3\alpha S)-2,3,3a,4,5,6\text{-Hexahydro-2-[(S)-1-Azabicyclo[2.2.2]oct-3-yl]2,3,3a,4,5,6-hexahydro-1-oxo-1Hbenz[e]isoquinoline, and is preferably present as the monohydrochloride. Palonosetron monohydrochloride can be represented by the following chemical structure:
Concentrations -- When concentrations of palonosetron are given herein, the concentration is measured in terms of the weight of the free base. Concentrations of all other ingredients are given based on the weight of ingredient added to the solution.

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

“Pharmaceutically acceptable salts” means salts which are pharmaceutically acceptable, as defined above, and which possess the desired pharmacological activity. Such salts include acid addition salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or with organic acids such as acetic acid, propionic acid, hexanoic acid, heptanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, o-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid p-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, p-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4′-methylenedioxy(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\textsuperscript{th} the amount of other previously known compounds for treating emesis, surprisingly allows the use of concentrations of palonosetron far below those that would ordinarily be expected. Thus, in one embodiment the invention provides a pharmaceutically stable solution for preventing or reducing emesis comprising a) from about 0.01 mg/mL to about 5 mg/mL palonosetron or a pharmaceutically acceptable salt thereof; and b) a pharmaceutically acceptable carrier. Similarly, in another embodiment the invention provides a method of formulating a pharmaceutically stable solution of palonosetron comprising admixing from about 0.01 mg/mL to about 5 mg/mL palonosetron or a pharmaceutically acceptable salt thereof; with a pharmaceutically acceptable carrier. In alternative embodiments, the formulation includes palonosetron or a pharmaceutically acceptable salt thereof in a concentration from about 0.02 mg/mL to about 1.0 mg/mL, from about 0.03 mg/mL to about 0.2 mg/mL, and most optimally about 0.05 mg/mL.

A particular advantage associated with the lower dosages of intravenous palonosetron is the ability to administer the drug in a single intravenous bolus over a short, discrete time period. This time period generally extends from about 10 to about 60 seconds, or about 10 to about 40 seconds, and most preferably is about 10 to 30 seconds. In one particular embodiment the palonosetron is supplied in vials that comprise 5 ml of solution, which equates to about 0.25 mg of palonosetron at a concentration of about 0.05 mg/ml.

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

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

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

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

Injectable formulations are typically formulated as aqueous solutions in which water is the primary excipient. Oral formulations will differ from injectable formulations generally by the additional presence of flavoring agents, coloring agents, or viscosity agents. Natural or synthetic sweeteners include, among others, mannitol, sorbitol, saccharose, saccharine, aspartame, acesulfame 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.

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>mg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palonosetron Hydrochloride</td>
<td>0.05*</td>
</tr>
<tr>
<td>Mannitol</td>
<td>41.5</td>
</tr>
<tr>
<td>Ingredient</td>
<td>mg/mL</td>
</tr>
<tr>
<td>------------------------------------</td>
<td>--------</td>
</tr>
<tr>
<td>Palonosetron Hydrochloride</td>
<td>0.05*</td>
</tr>
<tr>
<td>Mannitol</td>
<td>150</td>
</tr>
<tr>
<td>EDTA</td>
<td>0.5</td>
</tr>
<tr>
<td>Trisodium citrate</td>
<td>3.7</td>
</tr>
<tr>
<td>Citric acid</td>
<td>1.56</td>
</tr>
<tr>
<td>WFJ</td>
<td>q.s. to 1 ml</td>
</tr>
<tr>
<td>Sodium hydroxide solution and/or</td>
<td>pH 5.0 ± 0.5</td>
</tr>
<tr>
<td>hydrochloric acid solution</td>
<td></td>
</tr>
</tbody>
</table>

* 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.

**EXAMPLE 6 -- STABILITY OF PALONOSETRON WITHOUT DEXAMETHASONE**

The physical and chemical stability of palonosetron HCl was studies in concentrations of 5 µg/mL and 30 µg/mL in 5% dextrose injection, 0.9% sodium chloride injection, 5% dextrose in 0.45% sodium chloride injection, and dextrose 5% in lactated Ringer’s injection. The admixtures were evaluated over 14 days at 4 °C in the dark and for 48 hours at 23 °C under fluorescent light.
Test samples of palonosetron HCl were prepared in polyvinyl chloride (PVC) bags of the infusion solutions at concentrations of 5 and 30 µg/mL. Evaluations for physical and chemical stability were performed on samples taken initially and after 1, 3, 5, 7, and 14 days of storage at 4 °C and after 1, 4, 24, and 48 hours at 23 °C. Physical stability was assessed using visual observation in normal room light and using a high-intensity monodirectional light beam. In addition, turbidity and particle content were measured electronically. Chemical stability of the drug was evaluated by using a stability-indicating high performance liquid chromatographic (HPLC) analytical technique.

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

**EXAMPLE 7 -- STABILITY OF PALONOSETRON WITH DEXAMETHASONE**

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

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

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

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

What is claimed is:

1) 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.

2) The solution of claim 1 wherein the palonosetron or pharmaceutically acceptable salt thereof is in a concentration from about 0.02 mg/mL to about 1.0 mg/mL.

3) The solution of claim 1 wherein the palonosetron or pharmaceutically acceptable salt thereof is in a concentration from about 0.03 mg/mL to about 0.2 mg/mL.

4) The solution of claim 1 wherein the palonosetron or pharmaceutically acceptable salt thereof is in a concentration of about 0.05 mg/mL.

5) The solution of claim 1 comprising palonosetron hydrochloride.

6) The solution of claim 1 wherein the pH is from about 4.0 to about 6.0.

7) The solution of claim 1 wherein the pH is from about 4.5 to about 5.5.

8) The solution of claim 1 wherein the pharmaceutically acceptable carrier comprises a chelating agent.

9) The solution of claim 1 wherein the pharmaceutically acceptable carrier comprises from about 0.005 mg/ml to about 1.0 mg/ml EDTA.

10) The solution of claim 1 wherein the pharmaceutically acceptable carrier comprises mannitol.

11) The solution of claim 1 wherein the pharmaceutically acceptable carrier comprises from about 10 to about 100 milliMoles of a citrate buffer.

12) The solution of claim 1 adapted for intravenous administration.

13) The solution of claim 1 adapted for oral administration.

14) 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.

15) The solution of claim 14 wherein the pH is from about 4.5 to about 5.5.

16) The solution of claim 14 wherein the pH is about 5.0.

17) The solution of claim 14 wherein the palonosetron or pharmaceutically acceptable salt thereof is in a concentration from about 0.01 mg/mL to about 5.0 mg/mL.

18) The solution of claim 14 wherein the palonosetron or pharmaceutically acceptable salt thereof is in a concentration of about 0.05 mg/mL.

19) The solution of claim 14 wherein the pharmaceutically acceptable carrier comprises a chelating agent.

20) The solution of claim 14 wherein the pharmaceutically acceptable carrier comprises from about 0.005 mg/ml to about 1.0 mg/ml EDTA.

21) The solution of claim 14 wherein the pharmaceutically acceptable carrier comprises mannitol.

22) The solution of claim 14 wherein the pharmaceutically acceptable carrier comprises from about 10 to about 100 milliMoles of a citrate buffer.

23) The solution of claim 14 comprising palonosetron hydrochloride.

24) The solution of claim 14 further comprising sodium hydroxide or hydrochloric acid.

25) The solution of claim 14 adapted for intravenous administration.

26) The solution of claim 14 adapted for oral administration.

27) A pharmaceutically stable solution for preventing or reducing emesis comprising

   a) from about 0.01 to about 5.0 mg/ml palonosetron or a pharmaceutically acceptable salt thereof;

   b) from about 10 to about 100 millimoles citrate buffer; and
c) from about 0.005 to about 1.0 mg/ml EDTA.

28) The solution of claim 27 comprising about 0.05 mg/ml to of palonosetron hydrochloride.

29) The solution of claim 27 comprising from about 10 to about 40 milliMoles citrate buffer.

30) The solution of claim 27 comprising from about 0.3 to about 0.7 mg/ml of EDTA.

31) The solution of claim 27 adapted for intravenous administration.

32) The solution of claim 27 adapted for oral administration.

33) 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.

34) The solution of claim 33 wherein the chelating agent is EDTA.

35) The solution of claim 33 wherein the chelating agent is present in an amount from

about 0.005 mg/ml to about 1.0 mg/ml.

36) The solution of claim 33 wherein the chelating agent is present in an amount from

about 0.3 mg/ml to about 0.7 mg/ml.

37) The solution of claim 33 wherein the palonosetron or pharmaceutically acceptable

salt thereof is in a concentration from about 0.01 mg/mL to about 5.0 mg/mL.

38) The solution of claim 33 wherein the palonosetron or pharmaceutically acceptable

salt thereof is in a concentration of about 0.05 mg/mL.

39) The solution of claim 33 wherein the pharmaceutically acceptable carrier

comprises mannitol.

40) The solution of claim 33 wherein the pharmaceutically acceptable carrier

comprises from about 10 to about 100 milliMoles of a citrate buffer.

41) The solution of claim 33 comprising palonosetron hydrochloride.
42) The solution of claim 33 wherein the pH is from about 4.0 to about 6.0.
43) The solution of claim 33 wherein the pH is from about 4.5 to about 5.5.
44) The solution of claim 33 adapted for intravenous administration.
45) The solution of claim 33 adapted for oral administration.
46) 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 mannitol.
47) The solution of claim 46 wherein the mannitol is in a concentration from about
   10.0 mg/ml to about 80.0 mg/ml.
48) The solution of claim 46 wherein the mannitol is in a concentration from about
   40.0 mg/ml to about 45.0 mg/ml.
49) The solution of claim 46 wherein the palonosetron or pharmaceutically acceptable
   salt thereof is in a concentration from about 0.01 mg/mL to about 5.0 mg/mL.
50) The solution of claim 46 wherein the palonosetron or pharmaceutically acceptable
   salt thereof is in a concentration of about 0.05 mg/mL.
51) The solution of claim 46 wherein the pharmaceutically acceptable carrier
    comprises a chelating agent.
52) The solution of claim 46 wherein the pharmaceutically acceptable carrier
    comprises from about 0.005 mg/ml to about 1.0 mg/ml EDTA.
53) The solution of claim 46 wherein the pharmaceutically acceptable carrier
    comprises from about 10 to about 100 milliMoles of a citrate buffer.
54) The solution of claim 46 comprising palonosetron hydrochloride.
55) The solution of claim 46 wherein the pH is from about 4.0 to about 6.0.
56) The solution of claim 46 wherein the pH is from about 4.5 to about 5.5.
57) The solution of claim 46 adapted for intravenous administration.
58) The solution of claim 46 adapted for oral administration.

59) A pharmaceutically stable solution for preventing or reducing drug induced emesis comprising
   a) palonosetron or a pharmaceutically acceptable salt thereof and
   b) a pharmaceutically acceptable carrier,

   wherein the pharmaceutically acceptable carrier comprises from about 10 to about 100 milliMoles of a citrate buffer.

60) The solution of claim 59 wherein the pharmaceutically acceptable carrier comprises from about 10 to about 70 milliMoles of a citrate buffer.

61) The solution of claim 59 wherein the pharmaceutically acceptable carrier comprises from about 10 to about 40 milliMoles of a citrate buffer.

62) The solution of claim 59 wherein the palonosetron or pharmaceutically acceptable salt thereof is in a concentration from about 0.01 mg/mL to about 5.0 mg/mL.

63) The solution of claim 59 wherein the palonosetron or pharmaceutically acceptable salt thereof is in a concentration of about 0.05 mg/mL.

64) The solution of claim 59 wherein the pharmaceutically acceptable carrier comprises a chelating agent.

65) The solution of claim 59 wherein the pharmaceutically acceptable carrier comprises from about 0.005 mg/ml to about 1.0 mg/ml EDTA.

66) The solution of claim 59 wherein the pharmaceutically acceptable carrier comprises mannitol.

67) The solution of claim 59 comprising palonosetron hydrochloride.

68) The solution of claim 59 wherein the pH is from about 4.0 to about 6.0.

69) The solution of claim 59 wherein the pH is from about 4.5 to about 5.5.

70) The solution of claim 59 adapted for intravenous administration.

71) The solution of claim 59 adapted for oral administration.
72) 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 degrees celsius;

c) storing said containers in said room for one month or more,

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 mannitol or a chelating agent, or (v) the solution comprises from about 10 to about 100 milliMoles of a citrate buffer.

73) 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;

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 5.0 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 mannitol or a
chelating agent or mannitol, or (v) the solution comprises from about 10 to about 100 milliMoles of a citrate buffer.
**INTERNATIONAL SEARCH REPORT**

A. **CLASSIFICATION OF SUBJECT MATTER**

IPC 7 A61K31/4747 A61K9/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. **FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE

C. **DOCUMENTS CONSIDERED TO BE RELEVANT**

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<td>US 5 202 333 A (BERGER JACOB ET AL) 13 April 1993 (1993-04-13) cited in the application column 28, line 59-68; examples 10,11,13</td>
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X | Further documents are listed in the continuation of box C. |

X | Patent family members are listed in annex. |

* Special categories of cited documents:
  *A* document defining the general state of the art which is not considered to be of particular relevance
  *E* earlier document but published on or after the international filing date
  *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
  *O* document referring to an oral disclosure, use, exhibition or other means
  *P* document published prior to the international filing date but later than the priority date claimed
  *

Date of the actual completion of the international search: 21 April 2004

Date of mailing of the international search report: 06/05/2004

Name and mailing address of the ISA
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Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016

Authorized officer: Tardi, C

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INTERNATIONAL SEARCH REPORT

Box II  Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. □ Claims Nos.:
   because they relate to subject matter not required to be searched by this Authority, namely:

2. [x] Claims Nos.: 14-71
   because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
   see FURTHER INFORMATION sheet PCT/ISA/210

3. □ Claims Nos.:
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a),

Box III  Observations where unity of invention is lacking (Continuation of Item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. □ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. □ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. □ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. □ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

□ The additional search fees were accompanied by the applicant's protest,

□ No protest accompanied the payment of additional search fees.
Continuation of Box II.2

Claims Nos.: 14-71

In view of the large number and also the wording of the claims presently on file, which render it difficult, if not impossible, to determine the matter for which protection is sought, the present application fails to comply with the clarity and conciseness requirements of Article 6 PCT (see also Rule 6.1(a) PCT) to such an extent that a meaningful search is impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear and concise, namely claims 1–13 and 72–73.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.
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