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(54) LIQUID PHARMACEUTICAL FORMULATIONS OF PALONOSETRON
FLÜSSIGE PHARMAZEUTISCHE PALONOSETRONFORMULIERUNGEN
FORMULATIONS PHARMACÉUTIQUES LIQUIDES DE PALONOSETRON

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(56) References cited:

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The file contains technical information submitted after the application was filed and not included in this specification

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Description

FIELD OF THE INVENTION

[0001] The present invention relates to shelf-life stable liquid formulations of palonosetron that are especially useful in the preparation of injectable and oral medicaments in the form of pharmaceutical solutions comprising:

a) from 0.03 mg/ml to 0.2 mg/ml palonosetron hydrochloride and
b) a pharmaceutically acceptable carrier at a pH of from 4.0 to 6.0 comprising a chelating agent.

BACKGROUND OF THE INVENTION

[0002] Emesis is a devastating consequence of cytotoxic therapy, radiotherapy, and postoperative 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$_3$ (5-hydroxytryptamine) receptor antagonists has been developed that treat such emesis by antagonizing cerebral functions associated with the 5-HT$_3$ 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$_3$ 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.

[0003] 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$_3$ antagonist every day until the risk of emesis has substantially subsided. The present class of 5-HT$_3$ antagonists has not proven especially helpful meeting this need, however, because the 5-HT$_3$ 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.

[0004] Recently, clinical investigations have been made concerning palonosetron, a new 5-HT$_3$ 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$_3$ 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>WFJ</td>
<td>To 1.0 ml.</td>
</tr>
</tbody>
</table>

[0005] 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.


[0007] 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.

[0008] 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 also an 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, the invention provides a pharmaceutically stable solution for preventing or reducing emesis comprising a) from about 0.03 mg/mL to about 0.2 mg/mL palonosetron hydrochloride; and b) a pharmaceutically acceptable carrier at a pH of from 4.0 to 6.0 comprising a chelating agent.

The inventors have discovered that by adjusting the formulation's pH and/or excipient concentrations it is possible to increase the stability of palonosetron formulations. In another embodiment the invention provides a pharmaceutically stable solution for preventing or reducing emesis as defined above, also comprising 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 as defined above and also comprising

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, prefilled 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-1H]benz[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 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-ethanesulfonic 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, tertiobutylacetic 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 1/10th 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, the invention provides a pharmaceutically stable solution for preventing or reducing emesis comprising a) from about 0.03 mg/mL to about 0.2 mg/mL palonosetron hydrochloride and b) a pharmaceutically acceptable carrier at a pH of from 4.0 to 6.0 comprising a chelating agent. Similarly, in another embodiment the invention provides a method of formulating a pharmaceutically stable solution of palonosetron HCl comprising admixing from about 0.03 g/mL to about 0.2 mg/mL palonosetron hydrochloride and a pharmaceutically acceptable carrier at a pH of from 4.0 to 6.0 comprising a chelating agent.

In another embodiment the invention provides a pharmaceutically stable solution for preventing or reducing
emesis comprising from about 0.03 to about 0.2 mg/ml palonosetron HCl 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 in a pharmaceutically acceptable carrier at a pH of from 4.0 to 6.0. Similarly, in another embodiment the invention provides a method of formulating a pharmaceutically stable solution of palonosetron comprising admixing from about 0.03 to about 0.2 mg/ml palonosetron HCl 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 in a pharmaceutically acceptable carrier at a pH of from 4.0 to 6.0. 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 comprise palonosetron HCl in a concentration 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.

[0032] 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 HCl at a concentration from 0.03 mg/ml to 0.2 mg/ml b) a pharmaceutically acceptable carrier at a pH of from 4.0 to 6.0, 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 HCl at a concentration from 0.03 mg/ml to 0.2 mg/ml and b) a pharmaceutically acceptable carrier at a pH of from 4.0 to 6.0, 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.

[0033] 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, aceulsulphame 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 tonifying agent.

[0034] 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.

[0035] 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 celsius; 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 HCl is present in a concentration of from about 0.03 mg/mL to about 0.2 mg/mL, (ii) the pH of the solution is from about 4.0 to about 6.0, (iii) the solution comprises from about 10 to about 100 millimoles citrate buffer and from about 0.005 to about 1.0 mg/ml EDTA chelating agent.

[0036] 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 HCl is present in a concentration of from about 0.03 mg/mL to about 0.2 mg/mL, (ii) the pH of the solution is from about 4.0 to about 6.0, (iii) the solution comprises from about 10 to about 100 millimoles citrate buffer and from about 0.005 to about 1.0 mg/ml EDTA chelating agent.

5
EXAMPLES

EXAMPLE 1: STABILIZING pH

[0037] 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

[0038] 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

[0039] 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

[0040] 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>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 hydrochloric acid solution</td>
<td>pH 5.0 ± 0.5</td>
</tr>
</tbody>
</table>

* calculated as a free base

EXAMPLE : FORMULATION II

[0041] The following is a representative pharmaceutical formulation containing palonosetron that is useful for oral 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>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>
</tbody>
</table>

EXAMPLE 6 -- STABILITY OF PALONOSETRON WITHOUT DEXAMETHASONE

[0042] 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.

[0043] 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.

[0044] 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

[0045] 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.

[0046] 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.

[0047] 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.

Claims

1. A pharmaceutically stable solution for preventing or reducing emesis comprising:
   a) from 0.03 mg/mL to 0.2 mg/mL palonosetron hydrochloride and
   b) a pharmaceutically acceptable carrier at a pH of from 4.0 to 6.0 comprising a chelating agent

2. The solution of claim 1 wherein the palonosetron hydrochloride is in a concentration of 0.05 mg/mL.

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

4. The solution of claim 1 wherein the pharmaceutically acceptable carrier comprises from 0.005 mg/ml to 1.0 mg/ml EDTA.
5. The solution of claim 1 wherein the pharmaceutically acceptable carrier comprises mannitol.

6. The solution of claim 1 adapted for intravenous administration.

7. The solution of claim 1 adapted for oral administration.

8. The solution of one of the preceding claims which is present as one unit dose comprising 5 ml solution in a vial.

9. The solution of claim 1, comprising palonosetron hydrochloride, mannitol, 10 to 100 mmoles of a citrate buffer, and water, at a pH of from 4.5 to 5.5.

10. The solution of claim 9, comprising 0.05 mg/mL palonosetron hydrochloride, based upon the free base, 41.5 mg/mL mannitol, 0.5 mg/mL EDTA, 3.7 mg/mL trisodium citrate, 1.56 mg/mL citric acid, and water q.s. to 1 mL, a pH of from 4.5 to 5.5.

11. Use of (i) a pH of a solution of from 4.0 to 6.0, (ii) from 10 to 100 millimoles citrate buffer; (iii) from 0.005 to 1.0 mg/ml EDTA, and (iv) mannitol for providing stability to an injectable solution of palonosetron or a pharmaceutically acceptable salt thereof, wherein the palonosetron or pharmaceutical salt thereof is present at a concentration of from 0.03 mg/mL to 0.2 mg/mL.

**Patentansprüche**

1. Pharmazeutisch stabile Lösung zur Verhütung oder Verminderung von Emesis enthaltend:
   a) 0,03 mg/ml bis 0,2 mg/ml Palonosetronhydrochlorid und
   b) einen pharmazeutisch annehmbaren Träger mit einem pH-Wert von 4,0 bis 6,0 enthaltend einen Komplexbildner.

2. Lösung nach Anspruch 1, wobei das Palonosetronhydrochlorid in einer Konzentration von 0,05 mg/ml vorliegt.

3. Lösung nach Anspruch 1, wobei der pH 4,5 bis 5,5 ist.

4. Lösung nach Anspruch 1, wobei der pharmazeutisch annehmbare Träger 0,005 mg/ml bis 1,0 mg/ml EDTA enthält.

5. Lösung nach Anspruch 1, wobei der pharmazeutisch annehmbare Träger Mannitol enthält.


7. Lösung nach Anspruch 1 angepasst für orale Verabreichung.

8. Lösung nach einem der vorhergehenden Ansprüche, die als Einheitsdosis mit 5 ml Lösung in einem Gläschen vorliegt.

9. Lösung nach Anspruch 1, enthaltend Palonosetronhydrochlorid, Mannitol, 10 bis 100 mmol Citratpuffer und Wasser mit einem pH von 4,5 bis 5,5.

10. Lösung nach Anspruch 9, enthaltend 0,05 mg/ml Palonosetronhydrochlorid berechnet als freie Base, 41,5 mg/ml Mannitol, 0,5 mg/ml EDTA, 3,7 mg/ml Trinatriumcitrat, 1,56 mg/ml Citronensäure und Wasser auf 1 ml mit einem pH von 4,5 bis 5,5.

11. Verwendung von
   i) einem pH-Wert einer Lösung von 4,0 bis 6,0,
   ii) 10 bis 100 mmol Citratpuffer;
   iii) 0,005 bis 1,0 mg/ml EDTA und
   iv) Mannitol,

   um einer injizierbaren Lösung von Palonosetron oder einem pharmazeutisch annehmbaren Salz davon Stabilität
zu verleihen, wobei das Palonosetron oder ein pharmazeutisches Salz davon in einer Konzentration von 0,03 mg/ml bis 0,2 mg/ml vorhanden ist.

**Revendications**

1. Solution pharmaceutiquement stable destinée à prévenir ou réduire les vomissements, qui comprend :
   a) de 0,03 mg/mL à 0,2 mg/mL de chlorhydrate de palonosétron et
   b) un vecteur pharmaceutiquement acceptable à un pH de 4,0 à 6,0, comprenant un agent chélateur.

2. Solution selon la revendication 1, dans laquelle la concentration du chlorhydrate de palonosétron est de 0,05 mg/mL.

3. Solution selon la revendication 1, dans laquelle le pH est de 4,5 à 5,5.

4. Solution selon la revendication 1, dans laquelle le vecteur pharmaceutiquement acceptable comprend de 0,005 mg/mL à 1,0 mg/mL d’EDTA.

5. Solution selon la revendication 1, dans laquelle le vecteur pharmaceutiquement acceptable comprend du mannitol.

6. Solution selon la revendication 1, adaptée pour une administration par voie intraveineuse.

7. Solution selon la revendication 1, adaptée pour une administration par voie orale.

8. Solution selon l’une quelconque des revendications précédentes, qui est présente sous la forme d’une unité posologique comprenant 5 mL de solution dans un flacon.

9. Solution selon la revendication 1, qui comprend du chlorhydrate de palonosétron, du mannitol, un tampon citrate 10 à 100 mmoles, et de l’eau, à un pH de 4,5 à 5,5.

10. Solution selon la revendication 9, qui comprend 0,05 mg/mL de chlorhydrate de palonosétron, en se basant sur la base libre, 41,5 mg/mL de mannitol, 0,5 mg/mL d’EDTA, 3,7 mg/mL de citrate trisodique, 1,56 mg/mL d’acide citrique, et de l’eau q.s. jusqu’à 1 mL, à un pH de 4,5 à 5,5.

11. Utilisation (i) d’une solution ayant un pH compris entre 4,0 et 6,0 ; (ii) d’un tampon citrate 10 à 100 mmoles ; (iii) de 0,005 à 1,0 mg/mL d’EDTA ; et (iv) de mannitol, pour conférer une stabilité à une solution injectable de palonosétron ou d’un sel pharmaceutiquement acceptable de celui-ci, le palonosétron ou le sel pharmaceutiquement acceptable de celui-ci étant présent à une concentration de 0,03 mg/mL à 0,2 mg/mL.
REFERENCES CITED IN THE DESCRIPTION

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