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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	
Giorgio CALDERARI et al.	Group Art Unit: 1628
Application No.: 13/901,830	Examiner: Shirley V. GEMBEH
Filed: May 24, 2013	
For: LIQUID PHARMACEUTICAL FORMULATIONS OF PALONOSETRON	Confirmation No.: 3806

AMENDMENT AND RESPONSE TO OFFICE ACTION

Commissioner of Patents
United States Patent Office
Alexandria, Virginia

TROUTMAN SANDERS
Customer Number 06980

Dear Sir:

In response to the Office Action mailed November 22, 2013, please consider the following Remarks.

A Replacement Claim Set begins on page 2.

Remarks begin on page 4.

A Terminal Disclaimer is being filed concurrently herewith.

REPLACEMENT CLAIM SET

1-9) (CANCELLED)

10) (PREVIOUSLY PRESENTED) A pharmaceutical single-use, unit-dose formulation for intravenous administration to a human to reduce the likelihood of cancer chemotherapy-induced nausea and vomiting, comprising a 5 mL sterile aqueous isotonic solution buffered at a pH of 5.0 ± 0.5, said solution comprising:

palonosetron hydrochloride in an amount of 0.25 mg based on the weight of its free base;

optionally a chelating agent; and

from 10 mg/mL to 80 mg/mL mannitol,

wherein said formulation is stable at 24 months when stored at room temperature.

11) (PREVIOUSLY PRESENTED) The pharmaceutical formulation of claim 10, wherein said mannitol is in an amount of 41.5 mg/mL.

12) (PREVIOUSLY PRESENTED) The pharmaceutical formulation of claim 10, wherein said solution further comprises a chelating agent.

13) (PREVIOUSLY PRESENTED) The pharmaceutical formulation of claim 12, wherein said chelating agent is EDTA.

14) (PREVIOUSLY PRESENTED) The pharmaceutical formulation of claim 13, wherein said EDTA is in an amount of from 0.005 mg/mL to 1.0 mg/mL.

15) (PREVIOUSLY PRESENTED) The pharmaceutical formulation of claim 14, wherein said EDTA is in an amount of 0.5 mg/mL.

16) (PREVIOUSLY PRESENTED) The pharmaceutical formulation of claim 10, wherein said solution further comprises a citrate buffer.

17) (PREVIOUSLY PRESENTED) The pharmaceutical formulation of claim 16, wherein said citrate buffer is at a concentration of 20 millimolar.

18) (PREVIOUSLY PRESENTED) A pharmaceutical single-use, unit-dose formulation for intravenous administration to a human to reduce the likelihood of cancer chemotherapy-

induced nausea and vomiting, comprising a 5 mL sterile aqueous isotonic solution buffered at a pH of 5.0 ± 0.5, said solution comprising:

palonosetron hydrochloride in an amount of 0.25 mg based on the weight of its free base;

optionally a chelating agent; and

from 10 mg/mL to 80 mg/mL mannitol,

wherein said formulation is stable at 18 months when stored at room temperature.

19) (NEW) The pharmaceutical formulation of claim 18, wherein said mannitol is in an amount of 41.5 mg/mL.

20) (NEW) The pharmaceutical formulation of claim 18, wherein said solution further comprises a chelating agent.

21) (NEW) The pharmaceutical formulation of claim 20, wherein said chelating agent is EDTA.

22) (NEW) The pharmaceutical formulation of claim 21, wherein said EDTA is in an amount of from 0.005 mg/mL to 1.0 mg/mL.

23) (NEW) The pharmaceutical formulation of claim 21, wherein said EDTA is in an amount of 0.5 mg/mL.

24) (NEW) The pharmaceutical formulation of claim 18, wherein said solution further comprises a citrate buffer.

25) (NEW) The pharmaceutical formulation of claim 16, wherein said citrate buffer is at a concentration of 20 millimolar.

REMARKS

Claims 10-25 are currently pending in this application. Claims 1-9 were previously canceled without prejudice or disclaimer. Claims 10-18 were previously presented and are unamended. Claims 19-25 are newly presented. Because claims 19-25 mirror claims 11-17, but depend from claim 18 instead of claim 10, support for the new claims can be found in currently pending claims 11-17. No new matter is added by the amendment.

REJECTION UNDER 35 U.S.C. § 103

Claims 10-18 are rejected under pre-AIA[1] 35 U.S.C. § 103 as obvious over U.S. 5,202,333 to Berger et al. ("Berger") in view of Barton "Citric Buffer Calculation" (2000) ("Barton") and U.S. 6,284,749 to Castillo et al. ("Castillo"), and further in view of U.S. 5,854,270 to Gambhir ("Gambhir") as evidenced by Matsumoto et al. "Manual for Practical Pharmacy" (1989) ("Matsumoto"). Office Action at pp. 3-8.

As an initial matter, Applicants note that they have prosecuted several applications in the same family as this application. Those applications have resulted in patents directed toward pharmaceutically stable intravenous solutions of palonosetron hydrochloride, single-use unit-dose formulations of palonosetron hydrochloride, and methods of making single unit dose vials of palonosetron hydrochloride. *See, e.g.*, U.S. 7,947,724 (claiming "stable intravenous solution"); U.S. 8,598,219 (claiming "single-use, unit-dose formulation"); and U.S. 8,598,218 (claiming "method of manufacturing and terminally sterilizing").

Like the '219 patent, the current patent application claims a "single-use unit-dose formulation" of palonosetron hydrochloride. All of the claims also recite (directly or indirectly): (1) a 0.25 mg dose of palonosetron hydrochloride based on the weight of its free base; and (2) a palonosetron hydrochloride concentration of 0.05 mg/mL (*i.e.*, 0.25 mg in 5 mL). As argued

[1] Applicants respectfully submit that this case should be examined under post-AIA 35 U.S.C. § 103 because it claims priority to an application that presented a claim that has a priority date after March 16, 2013. *See also* the "AIA Status" section below. Nevertheless, Applicants do not believe that the AIA has any impact on the examination of this application based on the pending rejections.

below, Applicants respectfully submit that these features were not obvious when this invention was made, and that these features further support the patentability of the claimed invention.

A. The Rejection Fails to Consider the Invention as a Whole

Applicants disagree with the rejection firstly because the Office's primary reference, Berger, fails to suggest the claimed dose (0.25 mg), and hence, fails to account for the invention as a whole. As stated in MPEP 2142:

> To reach a proper determination under 35 U.S.C. 103, the examiner must step backward in time and into the shoes worn by the hypothetical "person of ordinary skill in the art" when the invention was unknown and just before it was made. In view of all factual information, the examiner must then make a determination whether the claimed invention "as a whole" would have been obvious at that time to that person. Knowledge of applicant's disclosure must be put aside in reaching this determination, yet kept in mind in order to determine the "differences," conduct the search and evaluate the "subject matter as a whole" of the invention. The tendency to resort to "hindsight" based upon applicant's disclosure is often difficult to avoid due to the very nature of the examination process. However, impermissible hindsight must be avoided and the legal conclusion must be reached on the basis of the facts gleaned from the prior art.

The Office Action does not account for the invention as a whole because it does not properly address the dose feature recited in the claims. The Office Action addresses the 0.05 mg/mL concentration, and the obviousness of this concentration in view of Berger. In particular, the Office Action concludes that Berger renders the 0.05 mg/mL concentration obvious because Berger teaches palonosetron concentrations "from 0.000001% w to 10% weight." Office Action at p. 4. However, the claims are not limited solely to concentration; they also impose limitations on the actual dose of palonosetron hydrochloride in the formulation based on the weight of the free base (*i.e.*, 0.25 mg). The claimed invention cannot be obvious unless the formulation as a whole, including the dose, would have been obvious, which for the reasons discussed in the remainder of this paper, it clearly is not.

Importantly, the palonosetron hydrochloride dose recited in the currently pending claims was addressed previously during the prosecution of the parent continuation-in-part application,

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