Attorney Docket No. 23278.2
PATENT

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Date: April 6, 2009

/Michelle D. Miller/
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application:			
Calderari, et al.		Examiner:	**Shirley V. Gembeh**
Serial No.	**11/186,311**	Art Unit:	**1614**
Filed:	**July 21, 2005**		
For:	**Liquid Pharmaceutical Formulations of Palonosetron**		

AMENDMENT AND RESPONSE TO OFFICE ACTION

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

In response to the Office Action mailed in the above-referenced application on October 6, 2008, please enter the following amendments and consider the following remarks.

Enclosed herewith are the following documents:

- Request is hereby made to extend the time for response to the Office Action of October 6, 2008 to and through April 6, 2009, comprising an extension of the shortened period of Three Months.
- The 132 statutory declaration of Daniele Bonadeo.
- The 132 statutory declaration of Valentino Stella.

Amendments to the claims begin on page 3. No new claims are presented. Claims 1-31, 35, 37, 38, 45, 47 and 51-79 are canceled. Claims 32, 39, 40, 41, and 42 are amended. After the amendments, claims 32-34, 36, 39-44, 46 and 48-50 are pending. Claims 32 and 42 are the only remaining independent claims. No new matter is added by the amendments.

Remarks begin on page 5.

REMARKS

The present claims are drawn towards pharmaceutically stable intravenous solutions of palonosetron. One of the key aspects of the claims in the requirement for a chelating agent. There is nothing in the prior art that would have motivated a skilled worker to employ a chelating agent such as EDTA in the formulation. In fact, the use of a chelating agent to stabilize this formulation produces unexpected surprising results because Applicant's earlier work with palonosetron suggested that it would not benefit from a chelating agent. As stated in paragraph 16 of the Bonadeo declaration: "The fact that EDTA improves the stability of palonosetron at all is somewhat surprising, given our earliest work with the molecule, in which palonosetron demonstrated comparable stability at 5 °C as it did at 60-100 °C. If the molecule were undergoing auto-oxidation (the typical reason for adding a chelating agent), one would expect the higher temperature to produce more radical initiators and a faster reaction and degradation." This is the exact same conclusion that Dr. Stella reached in paragraphs 15-17 of his declaration that was filed on January 9, 2009. There is nothing about palonosetron that suggests it would have benefitted from a chelating agent, or that would have motivated a skilled worker to use a chelating agent.

The Office Action states that the citric acid in the Berger '333 patent examples is a chelating agent, and that it it would have been obvious to use EDTA instead of the citric acid described in the Berger '333 examples. However, this argument assumes that Berger was using citric acid as a chelating agent when he most likely was using the citric acid to adjust the pH of the solution. As Dr. Stella explains in paragraph 10 of his declaration, the prior art does not teach that a chelating agent should be used with palonosetron because palonosetron "lacks any of the structural features that commonly favor structural degradation."

There is also nothing in the prior art that would have motivated a skilled worker to work with the low concentrations of palonosetron described in the claims. In fact, there are two surprising results associated with this low palonosetron concentration:

(1) The fact that palonosetron becomes more stable as its concentration decreases is surprising, as explained by Dr. Stella in paragraph 16 of his declaration, because

auto-oxidation reactions typically become more favorable as the palonosetron concentration is reduced;

(2) The fact that the chelating agent only works at the lower concentrations of palonosetron described in the claims is also surprising. There is apparently a synergistic relationship between the use of a chelating agent and palonosetron, that only exists at the low concentrations described in the claims. As stated in paragraph 15 of the Bonadeo declaration, "One notable observation from these results is that the presence of EDTA improves stability at low palonosetron concentrations, but actually decreases stability at high palonosetron HCl concentrations." The main prior art cited against this application is the Berger '333 patent, which describes formulations that have higher concentrations of palonosetron. The fact that a chelating agent does not stabilize palonosetron at the higher concentrations taught in the Berger '333 patent, but that it does at the concentrations claimed in this application, further supports the patentability of the present invention.

The Bonadeo declaration also presents evidence of the unexpected stabilizing effect of pH on the formulation. See Bonadeo declaration at par. 10 and Table 2.

TABLE 2. Palonosetron HCl 80 °C pH-Stability Study

pH at Room Temp.	pH at Reaction Temp.	Buffer	T_{90} (days)
2.0	2.0	0.01 M HCl	76
5.0	5.0	Acetate	Not determined. 99.2% remaining at 252 days
7.4	7.3	Phosphate	180
10	9.4	Carbonate	270

Again, this could not have been predicted from the Berger '333 formulation, which had a pH of 3.7. See Bonadeo Dec. at Table 5.

Finally, Claim 41 and 42 are now limited to a very specific formulation, based on the showing in paragraphs 20 and 21 of the attached declaration from Daniele Bonadeo. That declaration presents the following figure 2:

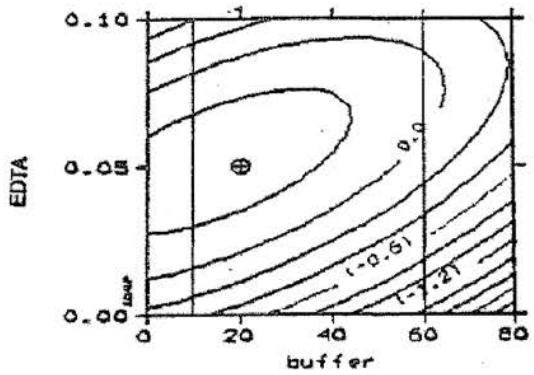

Figure 2

As explained in paragraph 21 of the Bonadeo declaration: "at the low palonosetron concentration depicted, there is a region of no apparent degradation with EDTA from 0.025 to 0.075 % w/v and buffer from 10 to 40 mM. This region is marked by the ⊕ symbol."

The formulation recited in claim 1 is limited to the region marked by a ⊕ symbol in Figure 2, and is almost exactly the same as the formulation shown in this figure, as the following table demonstrates:

Formulation of Claim 1	**Figure 2 Formulation; region denoted by ⊕ symbol**
Citrate buffer 10-40 millimoles	Citrate buffer 10-40 millimoles
EDTA 0.3-0.7 mg/ml	EDTA 0.025-0.075% w/v (i.e. 0.25-0.75 mg/ml)
Mannitol tonicifying agent	Mannitol tonicifying agent
pH 4.0-6.0	pH 5.0
Palonosetron 0.03-0.2 mg/ml	Palonosetron hydrochloride 0.4 mg/ml

Nothing in the prior art would have motivated a skilled worker to employ a citrate buffer and EDTA in the proportions described in claim 1. In fact, these proportions exhibit unexpected surprising results. It could not have been predicted that the combination of EDTA and buffer concentrations in the ⊕ region would produce the most stable formulation, especially in a formulation having a pH of 4-6, mannitol as the tonicifying agent, and a palonosetron concentration of 0.03-0.2 mg/ml

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