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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-372

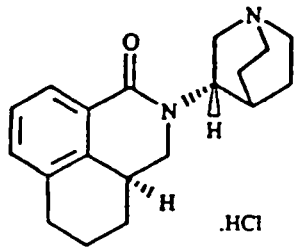
Medical Review(s)

Addendum: Medical Officer Review of NDA 21-372 Palonosetron

Date Submitted: 10 July 2003
Date Received: 11 July 2003
Date Completed: 11 July 2003

Applicant: Helsin Healthcare SA
Via Pian Scairolo
6912 Pazzallo (Lugano) - Switzerland

Drug: Generic Name - Palonosetron
Molecular Weight - 332.87
Molecular formula - $C_{19}H_{24}N_2O.HCl$
Molecular structure –



Drug Class: 5-HT_3 antagonists

Formulation: 5-ml vial of palonosetron injection contains 0.25 mg palonosetron base as hydrochloride, 207.5 mg mannitol, disodium edetate and citrate buffer in water

Route of Administration: Intravenous

I. Introduction

Helsinn Healthcare submitted a New Drug Application (NDA) for the new molecular entity palonosetron on September 26, 2002. The Medical Officer's Clinical Review for this NDA was completed June 6, 2003. Subsequently, it was noted that some of the data submitted by the applicant is contradictory and possibly erroneous. This data was included in the initial clinical review unaltered. The purpose of this document is to discuss the discrepancies in applicant submission and review the implications for the NDA as a whole.

II. Review of Data

The applicant's submission consisted of 381 volumes of written material. In two places (on page 220 of Volume 1, and page 99 of Volume 96) the following table can be found.

Table II:1 Number and Percentage of Patients with Post Dose* Changes in QTc by Bazett or Fridericia Corrections

	Palonosetron 0.25 mg (N = 605) Nt = 594		Palonosetron 0.75 mg (N = 610) Nt = 601		Ondansetron 32 mg (N = 410) Nt = 404		Dolasetron 100 mg (N = 194) Nt = 192	
	n	%	n	%	n	%	n	%
QTcB 30 to 60 msec	41	6	54	9	41	10	13	6
QTcB > 60 msec	5	0	3	0	7	1	2	1
QTcB > 500 msec	1	0	0	0	1	0	1	0
QTcF 30 to 60 msec	27	4	31	5	32	7	11	5
QTcF > 60 msec	5	0	2	0	4	1	1	0
QTcF > 500 msec	0	0	0	0	0	0	1	0

N= Number of patients in specific group.
Nt= Total Number of patients with ECG parameter.
n = Number of patients with changes.
% = Percentage of patients with changes.
QTcF = QT interval corrected by Fridericia formula.
QTcB = QT interval corrected by Bazett formula.
msec = Milliseconds
Source: Expert Report PALO-02-04; Appendix A.
* - post dose ECG's were obtained at 24 hours and 6-8 days after drug administration. A subset of patients had a ECG performed 15 minutes after drug administration. The data for this table was derived from the ECG that had the worst value for each patient regardless of the time of the recording.

The narrative accompanying this table goes on to state "no subject [in the palonosetron arms] had > 60 msec change from baseline." The table with the accompanying statement was incorporated in the Medical Officer's Clinical Review as Table 37 on page 77. Subsequently, it was noted that there were inconsistencies in this data. Firstly, the numbers and percentages do not correspond to each other. According to

this table, five subjects of 594 in the palonosetron 0.25 mg dose group had a change in QTcB > 60 msec. Yet, the table displays corresponding percentage as "0" rather than the correct percentage of 0.84. This happens several other times in this table for all the treatment arms. These instances where a "0" has inappropriately been listed as a percentage are shown in boldface type. In addition, the accompanying statement that no subjects had a QTc > 60 msec directly contradicts the information provided in the table.

On July 9, 2003 a telephone conversation was held between the medical officer from the Agency and Helsinn's representative Dr. Craig Lehmann to discuss these discrepancies. Consequently, Dr. Lehman spoke with Dr. —— the cardiologist who authored this portion of the NDA submission. The applicant provided a reply in the form of a phone message and written fax response on July 10, 2003. In the response, Dr. Lehmann verifies that the numbers listed in the "n" column of the table are correct. However, the percentages were not correct due to a rounding error. On review, it seems all the percentages for all the treatment arms were rounded down. The corrected version of the table is shown below.

Revised Table with Correct Percentages (rounded to nearest tenth)

	Palonosetron 0.25 mg (N = 605) Nt = 594		**Palonosetron 0.75 mg (N = 610) Nt = 601**		**Ondansetron 32 mg (N = 410) Nt = 404**		**Dolasetron 100 mg (N = 194) Nt = 192**	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**
QTcB 30 to 60 msec	41	6.9	54	8.9	41	10.1	13	6.7
QTcB > 60 msec	5	0.8	3	0.5	7	1.7	2	1.0
QTcB > 500 msec	1	0.2	0	0	1	0.2	1	0.5
QTcF 30 to 60 msec	27	4.5	31	5.2	32	7.9	11	5.7
QTcF > 60 msec	5	0.8	2	0.3	4	1	1	0.5
QTcF > 500 msec	0	0	0	0	0	0	1	0.5

N= Number of patients in specific group.
Nt= Total Number of patients with ECG parameter.
n = Number of patients with changes.
% = Percentage of patients with changes.
QTcF = QT interval corrected by Fridericia formula.
QTcB = QT interval corrected by Bazett formula.
msec = Milliseconds
Source: Expert Report PALO-02-04; Appendix A.

The applicant's response discusses the issues of the contradictory statement as follows "Based on discussion today with Dr. —— this statement reflects the zero percent incidence values which are incorrect as discussed." It appears the author referred to the erroneous percentage values when he stated that no patients had a change in QTc>60 msec. As the table shows 8 subjects in the palonosetron arms had QTcB changes > 60 msec and 7 subjects had QTcF changes > 60 msec.

The initial conclusion of the medical officer's clinical review in regard to cardiac safety was that palonosetron's effect on QTc was similar to that of other drugs in its class. These errors are not of a magnitude to alter this conclusion. Furthermore, the errors are of a mathematical nature and are present in all the treatment arms. They do not appear to be an attempt by the applicant to conceal or alter the side effect profile of this new molecular entity.

III. Summary

1. The percentages listed in Table III:1 entitled "Number and Percentage of Patients with Post Dose Changes in QTc by Bazett or Fridericia Corrections" is in error. This table was located on page 220 of Volume 1, and page 99 of Volume 96 in the NDA 21-372 submission for palonosetron. The table with the incorrect data was also incorporated in the Medical Officer's Clinical Review as Table 37 located on page 77. The corrected table can be found above.

2. The accompanying statement state "no subject had > 60 msec change from baseline" is also in error. This statement can be found in the narrative following the table on page 220 of Volume 1, and page 100 of Volume 96 in the NDA 21-372 for palonosetron. This incorrect statement was also incorporated into the Medical Officer's Clinical Review on page 77. The correct statement is that 8 subjects in the palonosetron arms had QTcB changes > 60 msec and 7 subjects in the palonosetron arms had QTcF changes of > 60 msec.

3. These errors are not of a magnitude to alter the medical officer's conclusion that palonosetron's effect on QTc is similar to that of other drugs in its class.

4. The errors appear to be of a mathematical nature, which are present in all the treatment arms. They do not appear to be a deliberate attempt by the applicant to conceal or alter the side effect profile of this new molecular entity.

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