CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-372/S008/S010

SUMMARY REVIEW

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research

DATE: 2/29/08

FROM: Joyce A Korvick, MD, MPH
DGP/ODE III

SUBJECT: Deputy Division Director Approval Recommendation
NDA 21-372
S-008: postoperative nausea and vomiting (PONV)
(b) (4)
S-010: removal of QTc prolongation warning information from the Warnings and Precautions section

APPLICANT: **Helsinn Healthcare SA**

DRUG: Aloxi® (palonosetron HCl) Injection
for Intravenous Use (0.075mg)

DIVISION RECOMMENDATION:
I recommend approval of S-008, and S-010, (b) (4)

Regulatory History:
The sponsor has applied for two indications:

a.) **(S-008)** prevention of postoperative nausea and vomiting (PONV) for up to (b) (4)
(b) (4)

The sponsor is also requesting removal of QTc prolongation warning information from the Warnings and Precautions section of the product labeling **(S-010).**

Aloxi is currently approved for CINV (Chemotherapy Induced Nausea and Vomiting) indications at a higher dose of 0.25 mg I.V. prior to chemotherapy. Since the terminal elimination half-life of Aloxi is longer than the other currently approved 5HT3 receptor antagonists (40 hours), it provides a potential advantage over the other compounds. Efficacy was sustained in the CINV indications for up to 120 hours. This duration is listed in the clinical trials section of the current label.

PONV (S-008) (b) (4) **INDICATIONS:**
This current application (S-008, (b) (4) addresses two indications PONV (b) (4)

In two randomized, phase 3 clinical studies (PALO-04-06 and PALO-04-07), at single doses of 0.025, 0.050 or 0.075 mg, palonosetron was compared with placebo for the prevention of PONV (b) (4) in 1090 patients undergoing laparoscopic abdominal or gynecological surgery (04- 06) or gynecological or breast surgery (04-07).

Two co-primary endpoints were used for the PONV (b) (4) indications; complete response (CR) from 0 to 24 hours, and CR from 24 to 72 hours. Relevant secondary endpoints, which studied CR at additional time intervals, were also considered. A statistical analysis plan detailed the handling of multiplicity for the primary endpoints but not for the secondary endpoints, thus the information is descriptive at best (for further details refer to Statistical Review).

The results are shown below for Study-06. Benefit was demonstrated for the 0.075 mg dose, which is the dose the sponsor is pursuing for approval. It is noted that this dose level failed to demonstrate statistical significance over placebo after from 24 to 72 hours. This is an important consideration I will return to later in this summary.

Prevention of Postoperative Nausea and Vomiting: Complete Response (CR), Study 1, Palonosetron 0.075 mg Vs Placebo

Treatment	n/N (%)	Palonosetron Vs Placebo	
		Δ	p-value*
Co-primary Endpoints			
CR 0-24 hours			
Palonosetron	59/138 (42.8%)	16.8%	0.004
Placebo	35/135 (25.9%)		
CR 24-72 hours			
Palonosetron	67/138 (48.6%)	7.8%	0.188
Placebo	55/135 (40.7%)		

* To reach statistical significance for each co-primary endpoint, the required significance limit for the lowest p-value was p<0.017.
ΔDifference (%): palonosetron 0.075 mg minus placebo

Study – 07, originally designated as a pivotal study, was submitted as a supportive study due to potential unblinding of the first 130 patients (approx. 30% of study participants). The sponsor provided a sensitivity analysis with the full data set including these patients as well as excluding these patients. When these patients were excluded efficacy results were not statistically significant (see statistical review for full details). Therefore, this study was not relied upon in the determination of efficacy in a substantial way.

The sponsor also provided a large phase two, double-blind, dose-ranging study (381 patients in the ITT population). This study demonstrated that the 1ug/kg dose (approximately 0.075mg) was the lowest effective dose. This study was well conducted.

For the PONV indication, Study-06, the Phase II dose-ranging study, and the CINV studies are the evidence upon which this indication will be granted. The pre-specified statistical analysis plan limits the proven efficacy to 24 hours post-surgery. It is important to note, that while not statistically significant, an analysis of 0-72 hours might be demonstrated if an additional study or studies were designed with an alternate statistical analysis plan. One hurdle associated with this strategy is the fact that most of the efficacy occurred in the first 24 hours; however, there may be patients at particular risk for PONV which might demonstrate benefit after 24 hours. (b) (4)

(b) (4)

The labeled indication was specifically written for 24 hour duration of efficacy:

"the prevention of postoperative nausea and vomiting (PONV) for up to 24 hours following surgery. Efficacy beyond 24 hours has not been demonstrated."

The Team Leader felt that it was important to specify this in the indication since clinicians have already come to expect a longer duration of effect for prevention of NV in the cancer population. (b) (4)

(b) (4)

(b) (4)

LABELING PONV (S-008): Thus, in labeling this drug we recommended approval of PONV as outlined above, with a description of the clinical trial which described the patients as abdominal laparoscopy "out-patients" (b) (4)

(b) (4) (b) (4)

(b) (4)

S-010: Requesting removal of QTc prolongation warning information from the Warnings and Precautions section of the product labeling.

The sponsor supplied a thorough QT study and safety analysis which was reviewed by the CDER QT Team. This study was well designed and conducted. The CDER Team concluded that:

"No significant effect of palonosetron administration on the QT interval was detected in this thorough QT study. The maximum increase (and corresponding upper two-sided 90% bound) in the placebo-corrected mean change in QTcI from baseline for the 0.25 mg, 0.75 mg and 2.25 mg dose groups were -0.6 ms (3.3 ms), 0.6 ms (5.1 ms) and 1 ms (4.8 ms). Similar results were observed for QTcF."

"Additionally, we recommend that the statement in the current label 'In non-clinical studies palonosetron possesses the ability to block ion channels involved in ventricular de- and re-polarization and to prolong action potential duration' be retained."

The team agreed with the final changes to the label regarding the QT wording (see final label attached to approval letter).

PEDIATRIC PREA:
We are waiving the pediatric study requirement for ages 0 to 1 month of age because necessary studies are impossible or highly impractical because there are too few children in this age group to study.
We are deferring submission of the sponsor's pediatric study for ages 1 month to 16 years for this application because the drug is ready for approval for use in adults and the pediatric studies have not been completed.

The Deferred pediatric study is a Post-Marketing commitment as follows:

1. Deferred pediatric study under PREA to evaluate (1) the safety and tolerability of two doses of I.V. palonosetron for the prevention of postoperative nausea and vomiting, and (2) the efficacy of these two I.V. palonosetron doses to prevent postoperative nausea and vomiting.

Final Report Submission: December 13, 2008

DMETS REVIEW:
Carton and Container labeling was reviewed and received very late in the review cycle. Discussions were held with the sponsor and it was agreed upon that they would make revisions accordingly, as outlined in the approval letter. One issue which was raised was the standardization of expression of palonosetron nomenclature and dosage strength. Proposed resolution is based upon the sponsors response dated February 29, 2008 in which they agreed to the following:

- Resolve the expression of palonosetron nomenclature and dosage strength on the carton label, container label, and in the package insert to present the milligram

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