CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-372/S008/S010

STATISTICAL REVIEW(S)

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U.S. Department of Health and Human Services
Food and Drug Administration
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STATISTICAL REVIEW AND EVALUATION
CLINICAL STUDIES

NDA/Ser Nr:	21372/S008/ (b) (4)
DATE RECEIVED:	April 27, 2007
PDUFA DATE:	March 4, 2008
DRUG NAME:	Aloxi (palonosetron HCL) Intravenous Injection
INDICATION:	Prevention of postoperative nausea and vomiting following elective abdominal or gynecological laparoscopic surgery
APPLICANT:	Helsinn Healthcare SA
REVIEW PRIORITY:	Standard
BIOMETRICS DIVISION:	Division of Biometrics 3 (HFD-725)
STATISTICAL REVIEWER:	Wen-Jen Chen, PhD
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MEDICAL DIVISION:	Gastroenterology Products (HFD-180)
CLINICAL TEAM:	Nancy Snow, MD, Hugo Gallo-Torres, MD (TL)
PROJECT MANAGER:	Jagjit Grewal, MPH
STATISTICAL KEYWORDS:	Clinical studies; NDA review; Multiplicity adjustments; Baseline adaptive randomization.

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1.0 EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

1.1 Conclusions and Recommendations

Based on review of the pivotal Study Palo-04-06 and the supportive Study Palo-04-07, palonosetron 0.075 mg is supported by substantial evidence of efficacy for use in prevention of postoperative nausea and vomiting for the first 24 hour postoperative observation period following elective abdominal or gynecological laparoscopic surgery.

1.2 Brief Overview of Clinical Studies

Two phase 3 Studies PALO-04-06 and PALO-04-07 were submitted by the applicant to support Aloxi for the prevention of postoperative nausea and vomiting (PONV) (b) (4)
(b) (4)
Supplement 008 refers to the PONV indication (b) (4)
(b) (4)

(b) (4)

For the PONV indication, due to partial unblinding of treatment codes, Study PALO-04-07 is considered a supportive study, and Study PALO-04-06 is considered a single principal study and thus required to show substantial evidence of efficacy, with the uncompromized data from the PALO-04-07 trial providing supportive evidence. However, based on that data, the applicant's efficacy analysis for study PALO-04-07 failed to show effectiveness of palonosetron over placebo for either the 0-24 or 24-72 hour periods for any of the dose groups (0.025 mg, 0.05 mg, and 0.075 mg). Thus the data from Study PALO-04-07 do not provide positive support for the pivotal Study PALO-04-06. (For more detail review of Study 07, refer to Section 2.1.2.)

Study PALO-04-06 was designed as a randomized, double-blind, multi-center, parallel group, placebo-controlled phase 3 trial to evaluate the efficacy and safety of single i.v. doses of palonosetron (0.025 mg, 0.050 mg, or 0.075 mg) versus placebo for the prevention of PONV from 0 to 24 hours and 24 to 72 hours in the post-operative period in male and female outpatients undergoing elective laparoscopic abdominal or gynecological surgery with general anesthesia. In this study, outpatients were defined as those expected to go home on the same day as surgery (no overnight stay). All laparoscopic procedures took place under general anesthesia.

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The population for this study consisted of eligible male or female outpatients with age ≥ 18, undergoing elective laparoscopic abdominal or gynecological surgery, who met the inclusion and not the exclusion criteria for the study and gave their informed consent to participate in the study.

The duration of this study was 12 and one-half months: first patient enrolled on 23 May 2005 and last patient completed on 12 June 2006. A total of 43 investigators from two countries (USA and Romania) participated in the study: 36 from USA and 7 from Romania.

The study drug was administered as a single i.v. dose of palonosetron or placebo for the prevention of PONV immediately (no more than 5 minutes) prior to induction of anesthesia (Study Day 1). In addition, efficacy and safety were assessed on the day of study drug administration at Visit 2 (Study Day 1) and at a final visit (Study Days 6 to 10) following the surgical procedure. The primary endpoint for this study was Complete Response (CR) defined as the absence of nausea and vomiting during the specified period.

The study had two co-primary objectives as follows:

1. To compare the effect of a single IV dose of palonosetron (0.025 mg, 0.050 mg or 0.075 mg) versus a single IV dose of placebo on CR during the first 24-hour postoperative observation period.
2. To compare the effect of a single IV dose of palonosetron (0.025 mg, 0.050 mg or 0.075 mg) versus a single IV dose of placebo on CR during the first 24-72 hour postoperative observation period.

A total of 639 patients were screened for this study, of which 574 patients were randomized into one of the four treatment arms: single i.v. doses of palonosetron (0.025 mg, 0.050 mg, or 0.075 mg) or placebo. A total of 547 patients were treated. The applicant used an adaptive randomization method to stratify and assign subjects to the four treatment groups in a 1:1:1:1 ratio.

1.3 Statistical Issues and Findings

1.3.1 Study PALO-04-06

For the first 24 hour observation period, superiority of palonosetron over placebo was demonstrated for the 0.05 and 0.075 mg dose groups showing efficacy evidence in prevention of postoperative nausea and vomiting following elective abdominal or gynecological laparoscopic surgery. However, the efficacy comparisons performed by the applicant for the 0.025 mg dose for the 0-24 hour period did not show superiority; and for the 24-72 hour postoperative observation period, all three palonosetron doses (0.025 mg, 0.05 mg, and 0.075 mg) failed to demonstrate superiority to placebo.

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