CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-372

Clinical Pharmacology and Biopharmaceutics Review

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-372	Submission Date: 09/27/02
Brand Name:	Aloxi
Generic Name:	Palonosetron Hydrochloride
Reviewers:	Sue-Chih Lee, Ph.D.
	Suliman Al-Fayoumi, Ph.D.
Team Leader:	Suresh Doddapaneni, Ph.D.
OCPB Division:	Division of Pharmaceutical Evaluation II
OND Division:	Division of Gastrointestinal and Coagulation Drug Products (HFD-180)
Sponsor:	Helsinn Healthcare SA (Switzerland)
Relevant IND(s):	[redacted]
Submission Type; Code:	NME, 1S
Formulation; Strength(s):	IV Injection, 0.25 mg/5 mL
Dosing regimen:	Single 0.25 mg dose, administered 30 minutes prior to chemotherapy
Proposed Indication:	Prevention of acute and delayed nausea and vomiting associated with initial and repeated courses of emetogenic cancer therapy

1. EXECUTIVE SUMMARY

Palonosetron is a novel 5-HT_3 receptor antagonist. The sponsor is seeking approval of single IV dose of palonosetron hydrochloride 0.25 mg for the prevention of acute and delayed nausea and vomiting associated with emetogenic cancer therapy, including highly emetogenic chemotherapy. To evaluate the potential QT effect of palonosetron following IV administration, the sponsor analyzed 12-lead ECG data collected from Phase 3 trials in which palonosetron was studied at two dose levels (0.25 mg and 0.75 mg). A subset of the patients also received Holter monitoring. Based on the overall QT data and cardiac safety profiles, the QT effect of palonosetron appears to be similar to the approved comparator drugs (dolasetron and ondansetron) used in the trials. Palonosetron is eliminated through both renal excretion and metabolic pathways with the latter mediated via multiple CYP isozymes. *In vitro* studies indicated that it does not inhibit or induce the activity of many CYP isozymes at the therapeutic concentrations. Therefore, the potential for drug interactions with palonosetron is low. No dosage adjustment is necessary based on age (18 yrs and up) or gender, nor is it necessary for any degree of

renal or hepatic impairment. Safety and efficacy in pediatric patients have not been established.

1.1 RECOMMENDATION

From the standpoint of the Office of Clinical Pharmacology and Biopharmaceutics, the Human Pharmacokinetics and Biopharmaceutics section of the application is acceptable provided that a satisfactory agreement is reached between the Agency and the sponsor regarding the language in the package insert.

/S/

Sue-Chih Lee, Ph.D.
Division of Pharmaceutical Evaluation II

/S/

Suliman Al-Fayoumi, Ph.D.
Division of Pharmaceutical Evaluation II

RD/FT Initialed by Suresh Doddapaneni, Ph.D. _____

2. TABLE OF CONTENTS

3. SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

3.1 Pharmacokinetics

3.1.1 Dose Proportionality

In a Phase 1 study, healthy subjects received a single IV dose of palonosetron. Both C_{max} and AUC were found to be approximately dose proportional over the dose range of 0.3-90 • g/kg.

3.1.2 Distribution

Following single IV administration to healthy volunteers, plasma palonosetron concentration exhibited a biphasic decline. The mean volume of distribution (V_z) was

8.34±2.45 L/kg. Protein binding in human plasma was constant over the concentration range of 5-412 ng/mL and averaged approximately 62%.

3.1.3 Metabolism

In vitro studies suggested that metabolism of palonosetron is mediated primarily via CYP2D6 followed by CYP3A4 and CYP1A2. The major metabolites are an N-oxide metabolite (M9; 12.5% of the administered dose) and a hydroxy metabolite (M4; 10.9% of the administered dose). The metabolites had negligible pharmacological activities.

3.1.4 Elimination

Both renal excretion and hepatic metabolism play important roles in the elimination of palonosetron. Following single IV administration of ^{14}C-palonosetron hydrochloride 10 • g/kg (0.7 mg/70 kg), renal clearance amounted to 42% of the total clearance while approximately 50% of the administered dose was metabolized. The mean terminal half-life based on a Phase 1 study was 37.4±14.2 hrs.

3.1.5 Special Populations

Age/Gender/Race

The disposition of palonosetron seemed to be similar between males and females after I.V. administration of a single dose of palonosetron to 6 healthy subjects (3 males and 3 females) in a mass balance study. A population PK analysis was performed using data obtained from the Phase III trials in which palonosetron was studied at two dose levels (0.25 mg and 0.75 mg). Age, gender and race were not found to be significant covariates for clearance. However, the final model yielded a high intersubject variability (88.8%) in clearance. Since analysis of the Phase III trial data did not reveal any subgroup with significant differences in the safety profiles, no dosage adjustment based on age or gender is considered necessary. It should be noted that Blacks were poorly represented in the Phase III trials. Hence, no conclusion can be made about PK in Blacks compared to Caucasians.

Renal insufficiency

Mean values of the primary PK parameters for palonosetron in patients with mild to moderate renal impairment were similar to those of healthy subjects. In patients with severe renal impairment, the mean $AUC_{0-\infty}$ increased by around 30% compared to healthy subjects. No dosage adjustment is recommended for patients with any degree of renal impairment.

Hepatic insufficiency

The mean values of C_{max} and AUC for palonosetron and the M9 metabolite were significantly reduced in patients with moderate and severe hepatic impairment relative to those of healthy subjects. Albeit the apparent half-life of palonosetron is prolonged by 50% in patients with moderate and severe hepatic impairment, dosage adjustment is not necessary as palonosetron will be administered as a single dose in the clinical setting.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.