CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-372/S008/S010

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Interdisciplinary Review Team for QT Studies
Response to a Request for Consultation: TQT Study Review

NDA	21372
Brand Name	Aloxi®
Generic Name	Palonosetron
Sponsor	Helsinn Healthcare SA
Drug Class	Selective serotonin subtype 3 ($5\text{-}HT_3$) receptor antagonist
Approved Indication	Prevention of chemotherapy induced nausea and vomiting (CINV)
Sought Indication	Prevention of postoperative nausea and vomiting (PONV)
Dosage Form	IV Solution
Therapeutic Doses	Chemotherapy Induced Nausea and Vomiting: • 0.25 mg injected intravenously over 30 seconds 30 minutes before starting chemotherapy Postoperative Nausea and Vomiting: • 0.075 mg injected intravenously over 10 seconds immediately before induction of anesthesia
Duration of Therapeutic Use	Acute
Application Submission Date	27 Jun 2007
Review Classification	TQT Study Report
Date Consult Received	28 Jun 2007
Clinical Division	DGP / HFD-180
PDUFA Date	01-September 2007

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

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.

The study was a randomized, double-blind, positive- and placebo-controlled parallel study in which 221 healthy subjects were administered single doses of palonosetron 0.25 mg, palonosetron 0.75 mg, palonosetron 2.25 mg, moxifloxacin 400 mg, or placebo. At the supratherapeutic dose (2.25 mg), palonosetron plasma concentrations were 9-fold

higher than concentrations following the therapeutic dose (0.25 mg). The plasma concentrations attained are sufficient to cover the increase in plasma concentrations expected due to known intrinsic factors.

A single dose of 400 mg moxifloxacin increased the QT interval by 11 ms (lower 95% confidence bound 8 ms) 2 hours after dosing indicating that the study was adequately designed and conducted to detect a mean increase in the QTc of about 5 ms.

1.2 ADDITIONAL QT INTERDISCIPLINARY REVIEW TEAM'S COMMENTS

1.2.1 Postmarketing experience

ICH E14 recommends post-marketing adverse event reports if available can be an additional source of information on a drug's proarrhythmic potential. The QT-IRT suggests that the division consider evaluating the postmarketing experience of ALOXI®.

1.2.2 Labeling

The QT-IRT suggests that the sponsor's proposed label be changed so that the final sentence state "The study demonstrated no ***significant*** effect on any ECG interval including QTc duration (cardiac repolarization) at doses up to 2.25 mg." Aloxi® has an effect on the QT interval but it is small. 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.

2 PROPOSED LABEL

The sponsor proposed the following label:

12. CLINICAL PHARMACOLOGY

12.2 Pharmacodynamics

The effect of palonosetron on QTc interval was evaluated in a double blind, randomized, parallel, placebo and positive (moxifloxacin) controlled trial in adult men and women. The objective was to evaluate the ECG effects of IV administered palonosetron at single doses of 0.25, 0.75 or 2.25 mg in 221 healthy subjects. (b) (4)

(b) (4)

The current label states:

"The effect of palonosetron on blood pressure, heart rate, and ECG parameters including QTc were comparable to ondansetron and dolasetron in clinical trials. 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. In clinical trials, the dose-response relationship to the QTc interval has not been fully evaluated."

"Although palonosetron has been safely administered to 192 patients with pre-existing cardiac impairment in the Phase 3 studies, ALOXI should be administered with caution in patients who have or may develop prolongation of

cardiac conduction intervals, particularly QTc. These include patients with hypokalemia or hypomagnesemia, patients taking diuretics with potential for inducing electrolyte abnormalities, patients with congenital QT syndrome, patients taking anti-arrhythmic drugs or other drugs which lead to QT prolongation, and cumulative high dose anthracycline therapy. In 3 pivotal trials, ECGs were obtained at baseline and 24 hours after subjects received palonosetron or a comparator drug. In a subset of patients ECGs were also obtained 15 minutes following dosing. The percentage of patients (<1%) with changes in QT and QTc intervals (either absolute values of > 500 ms or changes of > 60 ms from baseline) was similar to that seen with the comparator drugs."

3 BACKGROUND

Palonosetron is an antiemetic and antinauseant agent. It is a selective serotonin subtype 3 (5-HT_3) antagonist with a prolonged duration of action.

3.1 MARKET APPROVAL STATUS

ALOXI® (palonosetron) is approved in the USA for prevention of acute CINV associated with highly or moderately emetogenic chemotherapy and for prevention of delayed CINV associated with moderately emetogenic chemotherapy. The recommended dosage of ALOXI® is 0.25 mg administered as a single dose approximately 30 minutes before the start of chemotherapy. The sponsor has submitted a sNDA seeking approval to market ALOXI® for prevention of postoperative nausea and vomiting.

Palonosetron has also been approved for use for the prevention of chemotherapy induced nausea and vomiting (CINV) in 52 countries outside the US. Palonosetron has not been denied market approval in any country due to safety reasons, and palonosetron has not been withdrawn from the market in any country where it has been approved.

3.2 PRECLINICAL INFORMATION

The sponsor states the following in the Dec 2005 IB:

"Palonosetron inhibited hERG and hHNa channels stably expressed in HEK293 cells in a concentration dependent manner. The IC_{50} values were 1.9-2.04 µM and 6.5 µM for hERG and hHNa channels, respectively."

"In dog Purkinje fibers, Palonosetron induced a dose dependent increase in action potential duration (APD_{70} and APD_{90}) at 0.3 µM and 3.0 µM, under normal (60 ppm) and - to a larger extent - under low (12 ppm) stimulation rates, suggesting a reverse use-dependency."

"In conscious dogs administered Palonosetron by the intravenous route and monitored via telemetry for 24 hours (10 and 100 µg/kg) or 72 hours (1000 µg/kg), there were no pharmacologically relevant effects on arterial blood pressures, heart rate, PR interval, QRS complex duration, QT interval, QTc and in the frequency and occurrence of atrioventricular blocks."

3.3 PREVIOUS CLINICAL EXPERIENCE

The sponsor states in the Dec 2005 IB that through September 21, 2005, approximately (b) (4) vials of palonosetron have been sold worldwide and only one case of ventricular tachycardia has been reported (which is termed "unassessable")

Reviewer's comment: The QT-IRT did not review data from other portions of the current sNDA. Nor did the QT-IRT query AERS to assess if palonosetron is associated with an unusual frequency of adverse events that might be associated with QT-prolongation, i.e. sudden death, torsade de pointes, ventricular tachycardia, syncope, seizures, and QT prolongation.

3.4 CLINICAL PHARMACOLOGY

Table 1 summarizes the key features of palonosetron's clinical pharmacology.

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