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**APPLICATION NUMBER**

**21-372**

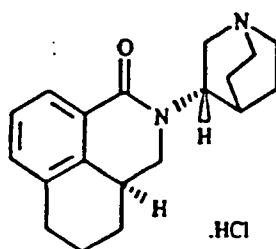
**Approved Labeling**

## Aloxi™ (Palonosetron Hydrochloride) Injection

### Helsinn Healthcare S.A. NDA 21-372 Palonosetron: Proposed Labeling

#### DESCRIPTION

Aloxi<sup>1</sup> (palonosetron hydrochloride) is an antiemetic and antinauseant agent. It is a selective serotonin subtype 3 (5-HT<sub>3</sub>) receptor antagonist with a strong binding affinity for this receptor. Chemically, palonosetron hydrochloride is: (3a*S*)-2-[(*S*)-1-Azabicyclo [2.2.2]oct-3-yl]-2,3,3a,4,5,6-hexahydro-1-oxo-1*H*benz[*de*]isoquinoline hydrochloride. The empirical formula is C<sub>19</sub>H<sub>24</sub>N<sub>2</sub>O.HCl, with a molecular weight of 332.87. Palonosetron hydrochloride exists as a single isomer and has the following structural formula:



Palonosetron hydrochloride is a white to off-white crystalline powder. It is freely soluble in water, soluble in propylene glycol, and slightly soluble in ethanol and 2-propanol.

Aloxi injection is a sterile, clear, colorless, non-pyrogenic, isotonic, buffered solution for intravenous administration. Each 5-ml vial of Aloxi injection contains 0.25 mg palonosetron base as hydrochloride, 207.5 mg mannitol, disodium edetate and citrate buffer in water for intravenous administration. The pH of the solution is 4.5 to 5.5.

#### CLINICAL PHARMACOLOGY

##### Pharmacodynamics

Palonosetron is a selective 5-HT<sub>3</sub> receptor antagonist with a strong binding affinity for this receptor and little or no affinity for other receptors.

Cancer chemotherapy may be associated with a high incidence of nausea and vomiting, particularly when certain agents, such as cisplatin, are used. 5-HT<sub>3</sub> receptors are located on the nerve terminals of the vagus in the periphery and centrally in the chemoreceptor trigger zone of the area postrema. It is thought that chemotherapeutic agents produce nausea and vomiting by releasing serotonin from the enterochromaffin cells of the small intestine and that the released serotonin then activates 5-HT<sub>3</sub> receptors located on vagal afferents to initiate the vomiting reflex.

<sup>1</sup> Pending trademark of Helsinn Healthcare SA  
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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.

### **Pharmacokinetics**

After intravenous dosing of palonosetron in healthy subjects and cancer patients, an initial decline in plasma concentrations is followed by a slow elimination from the body. Mean maximum plasma concentration ( $C_{max}$ ) and area under the concentration-time curve ( $AUC_{0-\infty}$ ) are generally dose-proportional over the dose range of 0.3–90  $\mu\text{g}/\text{kg}$  in healthy subjects and in cancer patients. Following single IV dose of palonosetron at 3  $\mu\text{g}/\text{kg}$  (or 0.21 mg/70 kg) to six cancer patients, mean ( $\pm$ SD) maximum plasma concentration was estimated to be  $5.6 \pm 5.5$  ng/mL and mean AUC was  $35.8 \pm 20.9$  ng·hr/mL.

### **Distribution**

Palonosetron has a volume of distribution of approximately  $8.3 \pm 2.5$  L/kg. Approximately 62% of palonosetron is bound to plasma proteins.

### **Metabolism**

Palonosetron is eliminated by multiple routes with approximately 50% metabolized to form two primary metabolites: N-oxide-palonosetron and 6-S-hydroxy-palonosetron. These metabolites each have less than 1% of the 5-HT<sub>3</sub> receptor antagonist activity of palonosetron. *In vitro* metabolism studies have suggested that CYP2D6 and to a lesser extent, CYP3A and CYP1A2 are involved in the metabolism of palonosetron. However, clinical pharmacokinetic parameters are not significantly different between poor and extensive metabolizers of CYP2D6 substrates.

### **Elimination**

After a single intravenous dose of 10  $\mu\text{g}/\text{kg}$  [<sup>14</sup>C]-palonosetron, approximately 80% of the dose was recovered within 144 hours in the urine with palonosetron representing approximately 40% of the administered dose. In healthy subjects the total body clearance of palonosetron was  $160 \pm 35$  mL/h/kg and renal clearance was  $66.5 \pm 18.2$  mL/h/kg. Mean terminal elimination half-life is approximately 40 hours.

### **Special Populations**

#### **Geriatrics**

Population PK analysis and clinical safety and efficacy data did not reveal any differences between cancer patients  $\geq 65$  years of age and younger patients (18 to 64 years). No dose adjustment is required for these patients.

### **Race**

Intravenous palonosetron pharmacokinetics was characterized in twenty-four healthy Japanese subjects over the dose range of 3 – 90 µg/kg. Total body clearance was 25% higher in Japanese subjects compared to Whites; however, no dose adjustment is required. The pharmacokinetics of palonosetron in Blacks has not been adequately characterized.

### **Renal Impairment**

Mild to moderate renal impairment does not significantly affect palonosetron pharmacokinetic parameters. Total systemic exposure increased by approximately 28% in severe renal impairment relative to healthy subjects. Dosage adjustment is not necessary in patients with any degree of renal impairment.

### **Hepatic Impairment**

Hepatic impairment does not significantly affect total body clearance of palonosetron compared to the healthy subjects. Dosage adjustment is not necessary in patients with any degree of hepatic impairment.

### **Drug-Drug Interactions**

Palonosetron is eliminated from the body through both renal excretion and metabolic pathways with the latter mediated via multiple CYP enzymes. Further *in vitro* studies indicated that palonosetron is not an inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2D6, CYP2E1 and CYP3A4/5 (CYP2C19 was not investigated) nor does it induce the activity of CYP1A2, CYP2D6, or CYP3A4/5. Therefore the potential for clinically significant drug interactions with palonosetron appears to be low.

A study in healthy volunteers involving single-dose IV palonosetron (0.75 mg) and steady state oral metoclopramide (10 mg four times daily) demonstrated no significant pharmacokinetic interaction.

In controlled clinical trials, Aloxi injection has been safely administered with corticosteroids, analgesics, antiemetics/antinauseants, antispasmodics and anticholinergic agents.

Palonosetron did not inhibit the antitumor activity of the five chemotherapeutic agents tested (cisplatin, cyclophosphamide, cytarabine, doxorubicin and mitomycin C) in murine tumor models.

## **CLINICAL STUDIES**

Efficacy of single-dose palonosetron injection in preventing acute and delayed nausea and vomiting induced by both moderately and highly emetogenic chemotherapy was studied in three Phase 3 trials and one Phase 2 trial. In these double-blind studies, complete response rates (no emetic episodes and no rescue medication) and other efficacy parameters were assessed through at least 120 hours after

administration of chemotherapy. The safety and efficacy of palonosetron in repeated courses of chemotherapy was also studied.

### **Moderately Emetogenic Chemotherapy**

Two Phase 3, double-blind trials involving 1132 patients compared single-dose IV Aloxi with either single-dose IV ondansetron (study 1) or dolasetron (study 2) given 30 minutes prior to moderately emetogenic chemotherapy including carboplatin, cisplatin  $\leq 50$  mg/m<sup>2</sup>, cyclophosphamide  $< 1500$  mg/m<sup>2</sup>, doxorubicin  $> 25$  mg/m<sup>2</sup>, epirubicin, irinotecan, and methotrexate  $> 250$  mg/m<sup>2</sup>. Concomitant corticosteroids were not administered prophylactically in study 1 and were only used by 4-6% of patients in study 2. The majority of patients in these studies were women (77%), White (65%) and naïve to previous chemotherapy (54%). The mean age was 55 years.

### **Highly Emetogenic Chemotherapy**

A Phase 2, double-blind, dose-ranging study evaluated the efficacy of single-dose IV palonosetron from 0.3 to 90  $\mu$ g/kg (equivalent to  $< 0.1$  mg to 6 mg fixed dose) in 161 chemotherapy-naïve adult cancer patients receiving highly-emetogenic chemotherapy (either cisplatin  $\geq 70$  mg/m<sup>2</sup> or cyclophosphamide  $> 1100$  mg/m<sup>2</sup>). Concomitant corticosteroids were not administered prophylactically. Analysis of data from this trial indicates that 0.25 mg is the lowest effective dose in preventing acute nausea and vomiting induced by highly emetogenic chemotherapy.

A Phase 3, double-blind trial involving 667 patients compared single-dose IV Aloxi with single-dose IV ondansetron (study 3) given 30 minutes prior to highly emetogenic chemotherapy including cisplatin  $\geq 60$  mg/m<sup>2</sup>, cyclophosphamide  $> 1500$  mg/m<sup>2</sup>, and dacarbazine. Corticosteroids were co-administered prophylactically before chemotherapy in 67% of patients. Of the 667 patients, 51% were women, 60% White, and 59% naïve to previous chemotherapy. The mean age was 52 years.

### **Efficacy Results**

The antiemetic activity of Aloxi was evaluated during the acute phase (0-24 hours) [Table 1], delayed phase (24-120 hours) [Table 2], and overall phase (0-120 hours) [Table 3] post-chemotherapy in Phase 3 trials.

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