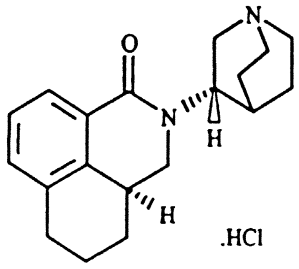
Aloxi™ (Palonosetron Hydrochloride) Injection

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

DESCRIPTION

Aloxi[1] (palonosetron hydrochloride) is an antiemetic and antinauseant agent. It is a selective serotonin subtype 3 (5-HT_3) receptor antagonist with a strong binding affinity for this receptor. Chemically, palonosetron hydrochloride is: (3aS)-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 $C_{19}H_{24}N_2O.HCl$, 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_3 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_3 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_3 receptors located on vagal afferents to initiate the vomiting reflex.

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[1] Pending trademark of Helsinn Healthcare SA
Lugano, Switzerland

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 µg/kg in healthy subjects and in cancer patients. Following single IV dose of palonosetron at 3 µg/kg (or 0.21 mg/70 kg) to six cancer patients, mean (±SD) maximum plasma concentration was estimated to be 5.6 ± 5.5 ng/mL and mean AUC was 35.8 ± 20.9 ng•hr/mL.

Distribution

Palonosetron has a volume of distribution of approximately 8.3 ± 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_3 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 µg/kg [^{14}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 ± 35 mL/h/kg and renal clearance was 66.5± 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 ≥ 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, CPY2D6, 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 ≤ 50 mg/m², cyclophosphamide < 1500 mg/m², doxorubicin > 25 mg/m², epirubicin, irinotecan, and methotrexate > 250 mg/m². 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 µg/kg (equivalent to < 0.1 mg to 6 mg fixed dose) in 161 chemotherapy-naïve adult cancer patients receiving highly-emetogenic chemotherapy (either cisplatin ≥ 70 mg/m² or cyclophosphamide > 1100 mg/m²). 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 ≥ 60 mg/m², cyclophosphamide > 1500 mg/m², 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.

Table 1: Prevention of Acute Nausea and Vomiting (0-24 hours): Complete Response Rates

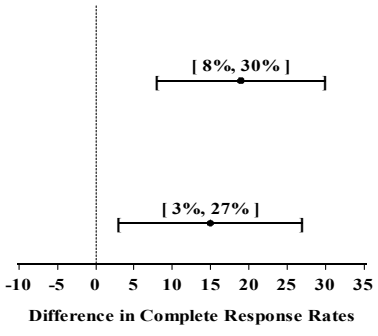
Chemo-therapy	Study	Treatment Group	N [a]	% with Complete Response	p-value [b]	97.5% Confidence Interval Aloxi minus Comparator [c]
Moderately Emetogenic	1	Aloxi 0.25 mg	189	81	0.009	[2%, 23%]
		Ondansetron 32 mg IV	185	69		[-2%, 22%]
	2	Aloxi 0.25 mg	189	63	NS	[-9%, 13%]
		Dolasetron 100 mg IV	191	53		
Highly Emetogenic	3	Aloxi 0.25 mg	223	59	NS	
		Ondansetron 32 mg IV	221	57		

-10 -5 0 5 10 15 20 25 30 35
Difference in Complete Response Rates

a Intent-to-treat cohort
b 2-sided Fisher's exact test. Significance level at α=0.025.
c These studies were designed to show non-inferiority. A lower bound greater than –15% demonstrates non-inferiority between Aloxi and comparator.

These studies show that Aloxi was effective in the prevention of acute nausea and vomiting associated with initial and repeat courses of moderately and highly emetogenic cancer chemotherapy. In study 3, efficacy was greater when prophylactic corticosteroids were administered concomitantly. Clinical superiority over other 5-HT3 receptor antagonists has not been adequately demonstrated in the acute phase.

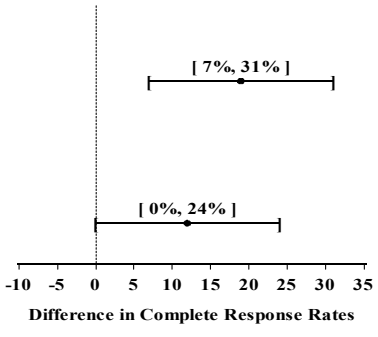
Table 2: Prevention of Delayed Nausea and Vomiting (24-120 hours): Complete Response Rates

Chemo-therapy	Study	Treatment Group	N [a]	% with Complete Response	p-value [b]	97.5% Confidence Interval Aloxi minus Comparator [c]
Moderately Emetogenic	1	Aloxi 0.25 mg	189	74	<0.001	
		Ondansetron 32 mg IV	185	55		
	2	Aloxi 0.25 mg	189	54	0.004	
		Dolasetron 100 mg IV	191	39		

a Intent-to-treat cohort
b 2-sided Fisher's exact test. Significance level at α=0.025.
c These studies were designed to show non-inferiority. A lower bound greater than –15% demonstrates non-inferiority between Aloxi and comparator.

These studies show that Aloxi was effective in the prevention of delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic chemotherapy.

Table 3: Prevention of Overall Nausea and Vomiting (0-120 hours): Complete Response Rates

Chemo-therapy	Study	Treatment Group	N [a]	% with Complete Response	p-value [b]	97.5% Confidence Interval Aloxi minus Comparator [c]
Moderately Emetogenic	1	Aloxi 0.25 mg	189	69	<0.001	
		Ondansetron 32 mg IV	185	50		
	2	Aloxi 0.25 mg	189	46	0.021	
		Dolasetron 100 mg IV	191	34		

a Intent-to-treat cohort
b 2-sided Fisher's exact test. Significance level at α=0.025.
c These studies were designed to show non-inferiority. A lower bound greater than –15% demonstrates non-inferiority between Aloxi and comparator.

These studies show that Aloxi was effective in the prevention of nausea and vomiting throughout the 120 hours (5 days) following initial and repeat courses of moderately emetogenic cancer chemotherapy.

INDICATIONS AND USAGE

Aloxi is indicated for:
1) the prevention of acute nausea and vomiting associated with initial and repeat courses of moderately and highly emetogenic cancer chemotherapy, and
2) the prevention of delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy.

CONTRAINDICATIONS

Aloxi is contraindicated in patients known to have hypersensitivity to the drug or any of its components.

PRECAUTIONS

General

Hypersensitivity reactions may occur in patients who have exhibited hypersensitivity to other selective 5-HT_3 receptor antagonists.

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 msec or changes of > 60 msec from baseline) was similar to that seen with the comparator drugs.

Drug Interactions

Palonosetron is eliminated from the body through both renal excretion and metabolic pathways. Therefore, the potential for clinically significant drug interactions with palonosetron appears to be low (See CLINICAL PHARMACOLOGY, Drug-Drug Interactions section).

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 104-week carcinogenicity study in CD-1 mice, animals were treated with oral doses of palonosetron at 10, 30 and 60 mg/kg/day. Treatment with palonosetron was not tumorigenic. The highest tested dose produced a systemic exposure to palonosetron (Plasma AUC) of about 150 to 289 times the human exposure (AUC= 29.8 ng•h/ml) at the recommended intravenous dose of 0.25 mg. In a 104-week carcinogenicity study in Sprague-Dawley rats, male and female rats were treated with oral doses of 15, 30 and 60 mg/kg/day and 15, 45 and 90 mg/kg/day, respectively. The highest doses produced a systemic exposure to palonosetron (Plasma AUC) of 137 and 308 times the human

exposure at the recommended dose. Treatment with palonosetron produced increased incidences of adrenal benign pheochromocytoma and combined benign and malignant pheochromocytoma, increased incidences of pancreatic Islet cell adenoma and combined adenoma and carcinoma and pituitary adenoma in male rats. In female rats, it produced hepatocellular adenoma and carcinoma and increased the incidences of thyroid C-cell adenoma and combined adenoma and carcinoma.

Palonosetron was not genotoxic in the Ames test, the Chinese hamster ovarian cell (CHO/HGPRT) forward mutation test, the ex vivo hepatocyte unscheduled DNA synthesis (UDS) test or the mouse micronucleus test. It was, however, positive for clastogenic effects in the Chinese hamster ovarian (CHO) cell chromosomal aberration test.
Palonosetron at oral doses up to 60 mg/kg/day (about 1894 times the recommended human intravenous dose based on body surface area) was found to have no effect on fertility and reproductive performance of male and female rats.

Pregnancy. Teratogenic Effects: Category B

Teratology studies have been performed in rats at oral doses up to 60 mg/kg/day (1894 times the recommended human intravenous dose based on body surface area) and rabbits at oral doses up to 60 mg/kg/day (3789 times the recommended human intravenous dose based on body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to palonosetron. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, palonosetron should be used during pregnancy only if clearly needed.

Labor and Delivery

Palonosetron has not been administered to patients undergoing labor and delivery, so its effects on the mother or child are unknown.

Nursing Mothers

It is not known whether palonosetron is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants and the potential for tumorigenicity shown for palonosetron in the rat carcinogenicity study, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in patients below the age of 18 years have not been established.

Geriatric Use

Of the 1374 adult cancer patients in clinical studies of palonosetron, 316 (23%) were ≥ 65 years old, while 71 (5%) were ≥ 75 years old. No overall differences in safety or effectiveness were observed between these subjects and the younger subjects but greater sensitivity in some older individuals cannot be ruled out. No dose adjustments or special monitoring are required for geriatric patients.

ADVERSE REACTIONS

In clinical trials for the prevention of nausea and vomiting induced by moderately or highly emetogenic chemotherapy, 1374 adult patients received palonosetron. Adverse reactions were similar in frequency and severity with Aloxi and ondansetron or dolasetron. Following is a listing of all adverse reactions reported by ≥ 2% of patients in these trials (Table 4).

Table 4: Adverse Reactions from Chemotherapy-Induced Nausea and Vomiting Studies ≥ 2% in any Treatment Group

Event	Aloxi 0.25 mg (N=633)	Ondansetron 32 mg IV (N=410)	Dolasetron 100 mg IV (N=194)
Headache	60 (9%)	34 (8%)	32 (16%)
Constipation	29 (5%)	8 (2%)	12 (6%)
Diarrhea	8 (1%)	7 (2%)	4 (2%)
Dizziness	8 (1%)	9 (2%)	4 (2%)
Fatigue	3 (< 1%)	4 (1%)	4 (2%)
Abdominal Pain	1 (< 1%)	2 (< 1%)	3 (2%)
Insomnia	1 (< 1%)	3 (1%)	3 (2%)

In other studies, 2 subjects experienced severe constipation following a single palonosetron dose of approximately 0.75 mg, three times the recommended dose. One patient received a 10 μg/kg oral dose in a post-operative nausea and vomiting study and one healthy subject received a 0.75 mg IV dose in a pharmacokinetic study.

In clinical trials, the following infrequently reported adverse reactions, assessed by investigators as treatment-related or causality unknown, occurred following administration of Aloxi to adult patients receiving concomitant cancer chemotherapy:

Cardiovascular: 1%: non-sustained tachycardia, bradycardia, hypotension, < 1%: hypertension, myocardial ischemia, extrasystoles, sinus tachycardia, sinus arrhythmia, supraventricular extrasystoles and QT prolongation . In many cases, the relationship to Aloxi was unclear.

Dermatological: < 1%: allergic dermatitis, rash.

Hearing and Vision: < 1% motion sickness, tinnitus, eye irritation and amblyopia.

Gastrointestinal system: 1%: diarrhea, < 1%: dyspepsia, abdominal pain, dry mouth, hiccups and flatulence.

General: 1%: weakness, < 1%: fatigue, fever, hot flash, flu-like syndrome.

Liver: < 1%: transient, asymptomatic increases in AST and/or ALT and bilirubin. These changes occurred predominantly in patients receiving highly emetogenic chemotherapy.

Metabolic: 1%: hyperkalemia, < 1%: electrolyte fluctuations, hyperglycemia, metabolic acidosis, glycosuria, appetite decrease, anorexia.

Musculoskeletal: < 1%: arthralgia.

Nervous System: 1%: dizziness, < 1%: somnolence, insomnia, hypersomnia, paraesthesia.

Psychiatric: 1%: anxiety, < 1%: euphoric mood.

Urinary System: < 1%: urinary retention.

Vascular: < 1%: vein discoloration, vein distention.

Overdosage

There is no known antidote to Aloxi. Overdose should be managed with supportive care. Fifty adult cancer patients were administered palonosetron at a dose of 90 μg/kg (equivalent to 6 mg fixed dose) as part of a dose ranging study. This is approximately 25 times the recommended dose of 0.25 mg. This dose group had a similar incidence of adverse events compared to the other dose groups and no dose response effects were observed. Dialysis studies have not been performed, however, due to the large volume of distribution, dialysis is unlikely to be an effective treatment for palonosetron overdose. A single intravenous dose of palonosetron at 30 mg/kg (947 and 474 times the human dose for rats and mice, respectively, based on body surface area) was lethal to rats and mice. The major signs of toxicity were convulsions, gasping, pallor, cyanosis and collapse.

DOSAGE AND ADMINISTRATION

Dosage for Adults

The recommended dosage of Aloxi is 0.25 mg administered as a single dose approximately 30 minutes before the start of chemotherapy. Repeated dosing of Aloxi™ within a seven day interval is not recommended because the safety and efficacy of frequent (consecutive or alternate day) dosing in patients has not been evaluated.

Use in Geriatric Patients and in Patients with Impaired Renal or Hepatic Function

No dosage adjustment is recommended.

Dosage for Pediatric Patients

A recommended intravenous dosage has not been established for pediatric patients.

Administration

Aloxi is to be infused intravenously over 30 seconds. Aloxi should not be mixed with other drugs. Flush the infusion line with normal saline before and after administration of Aloxi.

Stability

Parenteral drug products should be inspected visually for particulate matter and discoloration before administration, whenever solution and container permit.

HOW SUPPLIED

Aloxi (palonosetron hydrochloride), 0.25 mg (free base) in 5 ml, is supplied as a single-use sterile, clear, colorless solution in glass vials ready for intravenous injection.
Store at controlled temperature of 20–25°C (68°F–77°F). Excursions permitted to 15–30 °C (59-86°F). Protect from freezing. Protect from light.
NDC Number 58063-797-25
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