Attachment 1: Product information for AusPAR Aloxi Specialised Therapeutics Australia Pty Ltd PM-2012-02735-3-4 Final 7 January 2014. This Product Information was approved at the time this AusPAR was published.

PRODUCT INFORMATION

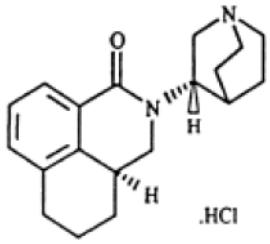
ALOXI

palonosetron HCl injection

NAME OF THE DRUG

ALOXI Injection
(palonosetron hydrochloride)

Structural Formula



DESCRIPTION

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.

Chemically, palonosetron hydrochloride is: (3aS)-2-[(S)-1-Azabicyclo[2.2.2]oct-3-yl]-2,3,3a,4,5,6-hexahydro-1-oxo-1Hbenz[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.

Chemical Abstracts Service (CAS) registry number:
135729-61-2 Palonosetron
135729-62-3 Palonosetron Hydrochloride

ALOXI injection is a sterile, clear, colourless, non-pyrogenic, isotonic, buffered solution for intravenous administration. Each 5 ml vial of ALOXI injection contains 250 µg equivalent palonosetron base as hydrochloride.

Inactive Ingredients:
Mannitol 207.5 mg, disodium edetate and citrate buffer in water for intravenous administration. The pH of the solution is 4.5 to 5.5.

PHARMACOLOGY

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.

Pharmacodynamics
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.

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. 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. The study demonstrated no effect on QT/QTc interval duration as well as any other ECG interval at doses up to 2.25 mg. No clinically significant changes were shown on heart rate, atrioventricular (AV) conduction and cardiac repolarisation.

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-oo}) 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.

Following intravenous administration of palonosetron 0.25 mg once every other day for 3 doses in 11 testicular cancer patients, the mean (± SD) increase in the initial phase of the plasma concentration-time curve ($AUC_{0-2.5hr}$) from Day 1 to Day 5 was 42 ± 34 %; how this finding relates to more conventional measures of systemic exposure is not known.

After intravenous administration of palonosetron 0.25 mg once daily for 3 days in 12 healthy subjects, the mean (± SD) increase in systemic exposure over 24 hours (AUC_{0-24hr}) from Day 1 to Day 3 was 110 ± 45 %.

Drug accumulation may be greater in the 10% of patients with prolonged elimination half-life.

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.

CLINICAL TRIALS

Single-dose palonosetron administration

Efficacy of single-dose palonosetron injection in preventing nausea and vomiting induced by moderately and highly emetogenic chemotherapy was studied in a phase 2 dose-ranging trial and three phase 3 trials. In the phase 3 trials, the primary efficacy endpoint was complete response rate (no emetic episodes and no rescue medication). Prevention of nausea was assessed as a secondary efficacy endpoint. 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 palonosetron 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, (age range 18-97).

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 250 µg 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 palonosetron 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. Highly emetogenic chemotherapy was given only for the first day of the chemotherapy cycle. For the remainder of the cycle, low to moderately (max grade 3 of Hesketh scale) emetogenic chemotherapy was allowed. 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; (age range 18-86).

Efficacy Results

Intent-to-treat analyses are presented. The conclusions of the per protocol analyses were similar.

Palonosetron was non-inferior to the comparators in the prevention of acute vomiting (within 24h) after moderately and highly emetogenic chemotherapy and comparable in the prevention of nausea (Tables 1-3). Efficacy was greater when corticosteroids were administered concomitantly in the highly emetogenic setting. The secondary efficacy endpoint of the study assessed delayed onset (24-120h) nausea and vomiting, the results are shown below (Tables 1-3). The comparative efficacy of palonosetron 250 µg in multiple cycles of chemotherapy has not been demonstrated.

Table 1: Study - Efficacy after Moderately Emetogenic Chemotherapy

	Palonosetron 250 µg (n=189)	Ondansetron 32 mg IV (n=185)	Difference [97.5%CI] [1]
Complete Response (%)			
0-24h	81.0	68.6	12.4[1.8.22.8]
24-120h	74.1	55.1	19.0[7.5,30.3]
0-120h	69.3	50.3	19.0[7.4,30.7]
No Nausea (%)			
0-24h	60.3	56.8	3.5[not sig]
24-120h	51.9	39.5	12.4[not sig]
0-120h	45.0	36.2	8.8[not sig]

Table 2: Study 2 - Efficacy after Moderately Emetogenic Chemotherapy

	Palonosetron 250 µg (n=189)	Dolasetron 100 mg IV (n=191)	Difference [97.5%CI][1]
Complete Response (%)			
0-24h	63.0	52.9	10.1 [-1.7,21.9]
24-120h	54.0	38.7	15.3 [3.4,27.1]
0-120h	46.0	34.0	12.0 [0.3,23.7]
No Nausea (%)			
0-24h	48.7	41.4	7.3 [not sig]
24-120h	41.8	26.2	15.6 [*p*=0.001]
0-120h	33.9	22.5	11.4[*p*=0.01]

Table 3: Study 3 - Efficacy after Highly Emetogenic Chemotherapy

	Palonosetron 250 µg (n=223)	Ondansetron 32 mg IV (n=221)	Difference [97.5%CI][1]
Complete Response (%)			
0-24h	59.2	57.0	2.2 [-8.8,13.1]
24-120h	45.3	38.9	6.4[-4.6,17.3]
0-120h	40.8	33.0	7.8[-2.9,18.5]
No Nausea (%)			
0-24h	53.8	49.3	4.5[not sig]
24-120h	35.4	32.1	3.3[not sig]
0-120h	33.6	32.1	1.5[not sig]

[1] The studies were designed to show non-inferiority in complete response. A lower bound > -15% demonstrates non-inferiority between palonosetron and comparator. Absence of nausea (Likert Scale) was compared using a Chi-square test at *p*=0.05 significance level.

Multiple-dose palonosetron administration

Published randomised, controlled studies have not been designed to show, or have not shown, improvement in primary efficacy endpoints related to nausea and vomiting in patient arms given ALOXI daily or on alternate days, relative to single dose use, in the context of multiple day chemotherapy. It has not been clearly established that such repeated dosing provides significant additional benefit compared to a single dose.

INDICATIONS

ALOXI is indicated for prevention of nausea and vomiting induced by cytotoxic 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. ALOXI should not be used to prevent or treat nausea and vomiting in the days following chemotherapy if not associated with another chemotherapy administration.

Cardiac Conduction

At all dose levels tested, palonosetron did not induce clinically relevant prolongation of the QTc interval. A specific thorough QT/QTc study was conducted in healthy volunteers for definitive data demonstrating the effect of palonosetron on QT/QTc (see *Pharmacodynamics*). However, as for the other 5-HT_3 antagonists, caution should be exercised in the concomitant use of palonosetron with medicinal products that increase the QT interval or in patients who have or are likely to develop prolongation of the QT interval.

Effects on ability to drive and use machines: No studies on the effects on the ability to drive and use machines have been performed.

Carcinogenicity

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 > 600 times the human exposure at the recommended intravenous dose of 250 µg.

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 lowest and highest doses, respectively, produced a systemic exposure to palonosetron (plasma AUC) of > 25 times and > 500 times the human exposure at the recommended dose.

Treatment with palonosetron produced increased incidences of adrenal benign pheochromocytoma and combined benign and malignant pheochromocytoma in both male and female rats, of pancreatic Islet cell adenoma and combined adenoma and carcinoma of pancreatic acinar cell adenoma and combined adenoma and adenocarcinoma and of pituitary adenoma in male rats. Increased incidences of skin keratocanthomas and tail squamous cell papillomas were also observed, mainly in males. In female rats, palonosetron produced hepatocellular adenoma and combined hepatocellular adenoma and carcinoma, and increased the incidences of thyroid C-cell adenoma and combined adenoma and carcinoma, and of mammary gland adrenocarcinoma.

Genotoxicity

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 test or the mouse micronucleus test. It was, however, positive for clastogenic effects in the CHO cell chromosomal aberration test.

Effects on Fertility

Palonosetron at oral doses of up to 60 mg/kg/day (>170 times the recommended human intravenous dose based on estimated plasma AUC) was found to have no effect on fertility and reproductive performance of male and female rats. Oral doses of 60 and 120 mg/kg/day given to male rats for 2 months prior to mating associated with complete infertility at the 120 mg/kg/day dose. Testicular degeneration was confirmed in a 3 month general toxicity study at oral doses of 60 and 120 mg/kg/day. An IV dose of up to 10 mg/kg/day (>250 times the recommended human intravenous dose based on plasma AUC) had no effect on male fertility and reproductive performance.

Special populations:

Geriatrics: Population pharmacokinetic 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.

Children: There are no data on efficacy and safety in patients below 18 years.

Use in Pregnancy (Category B1)
Palonosetron had no effect on foetal development at oral doses of up to 18 mg/kg/day in rats and 90 mg/kg/day in rabbits. At 60 and 120 mg/kg/day in rats, foetal weight was reduced. Palonosetron did not cause foetal abnormalities at these dose levels. However, palonosetron had toxic effects on the dams at 120 mg/kg in rats and 90 mg/kg/day in rabbits.

Because animal reproduction studies are not always predictive of human response, palonosetron should not be used during pregnancy unless it is considered essential.

Use during Lactation
It is not known whether palonosetron is excreted in human milk, but some other drugs of the same class are known to be excreted in rat milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue breastfeeding or to discontinue the drug, taking into account the importance of the drug to the mother.

INTERACTIONS WITH OTHER MEDICINES

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.

ADVERSE EVENTS

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 250 µg (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%)
Diarrhoea	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, pruritic rash.

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

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

General: 1%: weakness, asthenia < 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, hypocalcemia, hyperglycemia, metabolic acidosis, glycosuria, appetite decrease, anorexia.

Musculoskeletal: < 1%: arthralgia.

Nervous System: 1%: dizziness, < 1%: somnolence, insomnia, hypersomnia, paresthesia, and peripheral sensory neuropathy.

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

Urinary System: < 1%: urinary retention.

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

Post-marketing experience
In post-marketing reports there have been very rare cases of :

- Hypersensitivity reactions including anaphylaxis and shock, and
- Injection site reactions such as burning, induration, discomfort and pain

DOSAGE AND ADMINISTRATION

Dosage for Adults
The recommended dosage of ALOXI is 250 µg administered as a single dose approximately 30 minutes before the start of chemotherapy.

Drug accumulation was observed in subjects administered ALOXI on consecutive days or once every two days for three doses (see *Pharmacokinetics*). Safety and efficacy data available regarding repeated dosing of ALOXI within a course of multi-day chemotherapy are limited (see *Clinical Trial*s).

Use in Geriatric Patients and in Patients with Impaired Renal or Hepatic Function
No dosage adjustment is recommended.

Dosage for Paediatric Patients
A recommended intravenous dosage has not been established for paediatric patients.

Administration
ALOXI should only be used before chemotherapy administration. ALOXI is to be infused intravenously over 30 seconds.

Instructions for use/handling
Flush the infusion line with normal saline before and after administration of ALOXI.

Contains no antimicrobial agent. ALOXI is for single use in one patient only. Discard any residue.

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 250 µg. 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.

PRESENTATION AND STORAGE CONDITIONS

ALOXI 250 µg / 5 mL solution for injection is sold as a single pack of 1 vial.
Store below 25°C. Protect from light.

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE / MEDICINE SCHEDULE

S4 / Prescription Medicine

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