

Alox[®] Solution for Injection 50mcg/ml

Aloxi[®]

NAME OF THE MEDICINAL PRODUCT

Alox[®] Solution for Injection 50 mcg/ml

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution contains 50 micrograms of palonosetron hydrochloride equivalent to 50 micrograms (0.050 milligram) of palonosetron.

Each vial of 5 ml of Alox[®] contains 250 micrograms of palonosetron hydrochloride equivalent to 250 micrograms (0.25 milligram) of palonosetron.

Each vial of 1.5ml of Alox[®] contains 84 micrograms of palonosetron hydrochloride equivalent to 75 micrograms (0.075 milligram) of palonosetron.

For a full list of excipients, refer to *Pharmaceutical Particulars*.

PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless solution.

CLINICAL PARTICULARS

Therapeutic indications

Alox[®] is indicated for

Chemotherapy-Induced Nausea and Vomiting

Adults and Paediatric Patients 1 month of Age and Older

- the prevention of acute nausea and vomiting associated with highly emetogenic cancer chemotherapy.
- the prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy.

Postoperative Nausea and Vomiting

- Prevention of postoperative nausea and vomiting (PONV) for up to 24 hours following surgery. Efficacy beyond 24 hours has not been demonstrated.

As with other antiemetics, routine prophylaxis is not recommended in patients in whom there is little expectation that nausea and/or vomiting will occur postoperatively. In patients where nausea and vomiting must be avoided during the postoperative period, Alox[®] is recommended even where the incidence of postoperative nausea and/or vomiting is low.

Posology and method of administration

This medicinal product should be administered by a healthcare professional under appropriate medical supervision.

Posology

Adults

Chemotherapy-Induced Nausea and Vomiting

250 micrograms palonosetron administered as a single intravenous bolus approximately 30 minutes before the start of chemotherapy. Alox[®] should be injected over 30 seconds.

The efficacy of Alox[®] in the prevention of nausea and vomiting induced by highly emetogenic chemotherapy may be enhanced by the addition of a corticosteroid administered prior to chemotherapy.

Postoperative Nausea and Vomiting

75 micrograms palonosetron administered as a single intravenous bolus over 10 seconds immediately before the induction of anaesthesia

Paediatric population

Chemotherapy-Induced Nausea and Vomiting

Children and Adolescents (aged 1 month to 17 years): 20 micrograms/kg (the maximum total dose should not exceed 1500mcg) palonosetron administration as a single 15 minutes intravenous infusion beginning approximately 30 minutes before the start of chemotherapy.

The safety and efficacy of Alox[®] in children aged less than 1 month have not been established. No data are available.

Postoperative Nausea and Vomiting

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

Elderly population

No dose adjustment is necessary for the elderly.

Hepatic impairment

No dose adjustment is necessary for patients with impaired hepatic function.

Renal impairment

No dose adjustment is necessary for patients with impaired renal function.

No data are available for patients with end stage renal disease undergoing haemodialysis.

Method of administration

For intravenous use.

Contraindications

Alox[®] is contraindicated in patients known to have hypersensitivity to the drug or any of its components.

Warnings and precautions

Hypersensitivity

Hypersensitivity reactions may occur in patients who have exhibited hypersensitivity to other 5-HT₃ receptor antagonists.

Serotonin Syndrome

The development of serotonin syndrome has been reported with 5-HT₃ receptor antagonists. Most reports have been associated with concomitant use of serotonergic drugs (e.g., selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors, mirtazapine, fentanyl, lithium, tramadol, and intravenous methylene blue). Some of the reported cases were fatal. Serotonin syndrome occurring with overdose of another 5-HT₃ receptor antagonist alone has also been reported. The majority of reports of serotonin syndrome related to 5-HT₃ receptor antagonist use occurred in a post- anaesthesia care unit or an infusion center.

Symptoms associated with serotonin syndrome may include the following combination of signs and symptoms: mental status changes (e.g. agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g.tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, with or without gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Patients should be monitored for the emergence of serotonin syndrome, especially with concomitant use of Alox[®] and other serotonergic drugs. If symptoms of serotonin syndrome occur, discontinue Alox[®] and initiate supportive treatment. Patients should be informed of the increased risk of serotonin syndrome, especially if Alox[®] is used concomitantly with other serotonergic

drugs [see *Drug Interactions, Patient Counseling Information*].

Adverse Reactions

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Chemotherapy-Induced Nausea and Vomiting

Adults

In clinical trials for the prevention of nausea and vomiting induced by moderately or highly emetogenic chemotherapy, 1374 adult patients received by palonosetron. Adverse reactions were similar in frequency and severity with Alox[®] and ondansetron or dolasetron. Following is a listing of all adverse reactions reported by ≥2% of patients in these trials (Table 1).

Table 1: Adverse Reactions from Chemotherapy-Induced Nausea and Vomiting Studies ≥ 2% in any Treatment Group

Event	Alox [®] 0.25 mg (N=633)	Ondansetron 32 mg I.V. (N=410)	Dolasetron 100 mg I.V. (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 mcg/kg oral dose in a post-operative nausea and vomiting study and one healthy subject received a 0.75 mg I.V. 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 Alox[®] 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 Alox[®] 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, paresthesia.

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

Urinary System: < 1%: urinary retention.

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

Paediatrics

In a paediatric clinical trial for the prevention of chemotherapy-induced nausea and vomiting 163 cancer patients received a single 20mcg/kg (maximum 1.5mg) intravenous infusion of palonosetron 30 minutes before beginning the first cycle of emetogenic chemotherapy. Patients had a mean age of 8.4 years (range 2 months to 16.9 years) and were 46% male; and 93% white.

The following adverse reactions were reported for palonosetron:

Nervous System: <1%: headache, dizziness, dyskinesia. General: <1%: infusion site pain.

Dermatological: <1%: allergic dermatitis, skin disorder.

In the trial, adverse reactions were evaluated in paediatric patients receiving palonosetron for up to 4 chemotherapy cycles.

Postoperative Nausea and Vomiting

The adverse reactions cited in Table 2 were reported in ≥ 2% of adults receiving I.V. Alox[®] 0.075 mg immediately before induction of anesthesia in one phase 2 and two phase 3 randomized placebo-controlled trials. Rates of events between palonosetron and placebo groups were indistinguishable. Some events are known to be associated with, or may be exacerbated by concomitant perioperative and intraoperative medications administered in this surgical population. Please refer to Pharmacological Properties Section, thorough QT/QTc study results, for definitive data demonstrating the lack of palonosetron effect on QT/QTc.

Table 2: Adverse Reactions from Postoperative Nausea and Vomiting Studies ≥ 2% in any Treatment Group

Event	Alox [®] 0.075 mg (N=336)	Placebo (N=369)
Electrocardiogram QT prolongation	16 (5%)	11 (3%)
Bradycardia	13 (4%)	16 (4%)
Headache	11 (3%)	14 (4%)
Constipation	8 (2%)	11(3%)

In these clinical trials, the following infrequently reported adverse reactions, assessed by investigators as treatment-related or causality unknown, occurred following administration of Alox[®] to adult patients receiving concomitant perioperative and intraoperative medications including those associated with anesthesia:

Cardiovascular: 1%: electrocardiogram QTc prolongation, sinus bradycardia, tachycardia; < 1%: blood pressure decreased, hypotension, hypertension, arrhythmia, ventricular extrasystoles, generalized edema; ECG T wave amplitude decreased, platelet count decreased. The frequency of these adverse effects did not appear to be different from placebo.

Dermatological: 1%: pruritus.

Gastrointestinal System: 1%: flatulence, < 1%: dry mouth, upper abdominal pain, salivary hypersecretion, dyspepsia, diarrhea, intestinal hypomotility, anorexia.

General: < 1%: chills.

Liver: 1%: increases in AST and/or ALT < 1%: hepatic enzyme increased.

Metabolic: < 1%: hypokalemia, anorexia.

Nervous System: < 1%: dizziness.

Respiratory: < 1%: hypoventilation, laryngospasm.

Urinary System: 1%: urinary retention.

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Alox[®]. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Very rare cases (<1/10,000) of hypersensitivity reactions and injection site reactions (burning, induration, discomfort and pain) were reported from post-marketing experience of Alox[®] 0.25 mg in the prevention of chemotherapy-induced nausea and vomiting.

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.

Serotonin syndrome (including altered mental status, autonomic instability, and neuromuscular symptoms) has been described following the concomitant use of 5-HT₃ receptor antagonists and other serotonergic drugs, including selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs) [see *Warnings and Precautions*].

Coadministration of 0.25 mg I.V. palonosetron and 20 mg I.V. dexamethasone in healthy subjects revealed no pharmacokinetic drug-interactions between palonosetron and dexamethasone.

In an interaction study in healthy subjects where palonosetron 0.25 mg (I.V. bolus) was administered on day 1 and oral aprepitant for 3 days (125 mg/80 mg/80 mg), the pharmacokinetics of palonosetron were not significantly altered (AUC: no change, C_{max}: 15% increase).

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

In controlled clinical trials, Alox[®] injection has been safely administered with corticosteroids, analgesics, antiemetics/anti-nauseants, 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.

USE IN SPECIFIC POPULATIONS

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.

Paediatric Use

Chemotherapy-Induced Nausea and Vomiting

Safety and effectiveness of ALOXI have been established in paediatric patients aged 1 month to less than 17 years for the prevention of acute nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including highly emetogenic cancer chemotherapy. Use is supported by a clinical trial where 165 paediatric patients aged 2 months to <17 years were randomized to receive a single dose of palonosetron 20 mcg/kg (maximum 1.5 mg) administered as an intravenous infusion 30 minutes prior to the start of emetogenic chemotherapy (see *Clinical Studies*). While this study demonstrated that paediatric patients require a higher palonosetron dose than adults to prevent chemotherapy-induced nausea and vomiting, the safety profile is consistent with the established profile in adults (see *Adverse Reactions*).

Safety and effectiveness of ALOXI in neonates (less than 1 month of age) have not been established.

Postoperative Nausea and Vomiting Studies

Safety and efficacy have not been established in paediatric patients for prevention of postoperative nausea and vomiting. Two paediatric trials were performed.

Paediatric Study 1, a dose finding study was conducted to compare two doses of palonosetron, 1 mcg/kg (max 0.075 mg) versus 3 mcg/kg (max 0.25 mg). A total of 150 paediatric surgical patients participated, age range 1 month to <17 years. No dose response was observed.

Paediatric Study 2, a multicenter, double-blind, double-dummy, randomized, parallel group, active control, single-dose non-inferiority study, compared I.V. palonosetron (1 mcg/kg, max 0.075 mg) versus I.V. ondansetron. A total of 670 paediatric surgical patients participated, age 30 days to <17 years. The primary efficacy endpoint, Complete Response (CR: no vomiting, no retching, and no antiemetic rescue medication) during the first 24 hours postoperatively was achieved in 78.2% of patients in the palonosetron group and 82.7% in the ondansetron group. Given the pre-specified non-inferiority margin of -10%, the stratum adjusted Mantel-Haenszel statistical non-inferiority confidence interval for the difference in the primary endpoint, complete response (CR), was [-10.5, 1.7%], therefore non-inferiority was not demonstrated. Adverse reactions to palonosetron were similar to those reported in

adults (see Table 2)

Geriatric Use

Population pharmacokinetics analysis did not reveal any differences in palonosetron pharmacokinetics between cancer patients ≥ 65 years of age and younger patients (18 to 64 years). 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 adjustment or special monitoring are required for geriatric patients.

Of the 1520 adult patients in Alox[®]PONV clinical studies, 73 (5%) were ≥ 65 years old. No overall differences in safety were observed between older and younger subjects in these studies, though the possibility of heightened sensitivity in some older individuals cannot be excluded. No differences in efficacy were observed in geriatric patients for the CINV indication and none are expected for geriatric PONV patients. However, Alox[®] efficacy in geriatric patients has not been adequately evaluated.

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.

Race

Intravenous palonosetron pharmacokinetics was characterized in twenty-four healthy Japanese subjects over the dose range of 3 – 90 mcg/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.

Overdosage

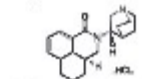
There is no known antidote to Alox[®]. Overdose should be managed with supportive care.

Fifty adult cancer patients were administered palonosetron at a dose of 90 mcg/kg (equivalent to 8 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.

DESCRIPTION

Alox[®] (palonosetron hydrochloride) is an antiemetic and antinauseant agent. It is a serotonin subtype 3 (5-HT₃) 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-1H-benz[de]isoquinoline hydrochloride. The empirical formula is C₁₆H₁₆N₂O.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.

Alox[®] injection is a sterile, clear, colorless, non pyrogenic, isotonic, buffered solution for intravenous administration. Alox[®] injection is available as 5 mL single use vial or 1.5 mL single use vial. Each 5 mL vial contains 0.25 mg palonosetron base as 0.28 mg palonosetron hydrochloride, 207.5 mg mannitol, disodium edetate and citrate buffer in water for intravenous administration.

Each 1.5 mL vial contains 0.075 mg palonosetron base as 0.084 mg palonosetron hydrochloride, 83 mg mannitol, disodium edetate and citrate buffer in water for intravenous administration.

The pH of the solution in the 5 mL and 1.5 mL vials is 4.5 to 5.5.

CLINICAL PHARMACOLOGY

Mechanism of Action

Palonosetron is a 5-HT₃ 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-HT₃ 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-HT₃ receptors located on vagal afferents to initiate the vomiting reflex.

Postoperative nausea and vomiting is influenced by multiple patient, surgical and anesthesia related factors and is triggered by release of 5-HT in a cascade of neuronal events involving both the central nervous system and the gastrointestinal tract. The 5-HT₃ receptor has been demonstrated to selectively participate in the emetic response.

Pharmacodynamics

The effect of palonosetron on blood pressure, heart rate, and ECG parameters including QTc were comparable to ondansetron and dolasetron in CINV clinical trials. In PONV clinical trials the effect of palonosetron on the QTc interval was no different from placebo. 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 I.V. administered palonosetron at single doses of 0.25, 0.75 or 2.25 mg in 221 healthy subjects. The study demonstrated no significant effect on any ECG interval including QTc duration (cardiac repolarization) at doses up to 2.25 mg.

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-∞}) are generally dose-proportional over the dose range of 0.3–90 mcg/kg in healthy subjects and in cancer patients. Following single I.V. dose of palonosetron at 3 mcg/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·h/mL.

Following I.V. administration of palonosetron 0.25 mg once every other day for 3 doses in 11 cancer patients, the mean increase in plasma palonosetron concentration from Day 1 to Day 5 was 42±34%. Following I.V. administration of palonosetron 0.25 mg once daily for 3 days in 12 healthy subjects, the mean (±SD) increase in plasma

palonosetron concentration from Day 1 to Day 3 was 110±45%. After intravenous dosing of palonosetron in patients undergoing surgery (abdominal surgery or vaginal hysterectomy), the pharmacokinetic characteristics of palonosetron were similar to those observed in cancer patients.

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-HT₃ receptor antagonist activity of palonosetron. *In vitro* metabolism studies have suggested that CYP2D6 and to a lesser extent, CYP3A4 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 mcg/kg [¹⁴C]-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.

Specific populations
Pediatric patients
Single-dose I.V. ALOXI pharmacokinetic data was obtained from a subset of pediatric cancer patients that received 10 mcg/kg or 20 mcg/kg. When the dose was increased from 10 mcg/kg to 20 mcg/kg a dose-proportional increase in mean AUC was observed. Following single dose intravenous infusion of ALOXI 20 mcg/kg, peak plasma concentrations (C_T) reported at the end of the 15 minute infusion were highly variable in all age groups and tended to be lower in patients < 6 years than in older patients. Median half-life was 29.5 hours in overall age groups and ranged from about 20 to 30 hours across age groups after administration of 20 mcg/kg.

The total body clearance (L/h/kg) in patients 12 to 17 years old was similar to that in healthy adults. There are no apparent differences in volume of distribution when expressed as L/kg.

Table 3: Pharmacokinetics Parameters in Pediatric Cancer Patients following intravenous infusion of ALOXI at 20 mcg/kg over 15 min

PK Parameter *	Paediatric Age Group			
	<2 y	2 to <6 y	6 to <12 y	12 to <17 y
	N=12	N=42	N=38	N=44
CT ^b , ng/L	9025 (197)	9414 (252)	16275 (203)	11831 (176)
		N=5	N=7	N=10
AUC ₀₋₂₄ , h·mcg/L		103.5 (40.4)	98.7 (47.7)	124.5 (19.1)
	N=6	N=14	N=13	N=19
Clearance ^c , L/h/kg	0.31 (34.7)	0.23 (51.3)	0.19 (46.8)	0.16 (27.8)
V _{ss} , L/kg	6.08 (36.5)	5.29 (57.8)	6.26 (40.0)	6.20 (29.0)

a Geometric Mean (CV) except for t_{1/2} which is median values
b CT is the plasma palonosetron concentration at the end of the 15 minute infusion
c Clearance and V_{ss} calculated from 10 and 20 mcg/kg and are weight adjusted

NONCLINICAL TOXICOLOGY

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.

CLINICAL STUDIES

Chemotherapy-Induced Nausea and Vomiting in Adults

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 assessed.

Moderately Emetogenic Chemotherapy

Two Phase 3, double-blind trials involving 1182 patients compared single-dose I.V. ALOXI with either single-dose I.V. 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 naive 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 I.V. palonosetron from 0.3 to 90 mcg/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 I.V. ALOXI with single-dose I.V. 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 4], delayed phase (24-120 hours) [Table 5], and overall phase (0-120 hours) [Table 6] post-chemotherapy in Phase 3 trials.

Table 4 Prevention of Acute Nausea and Vomiting (0-24 hours): Complete Response Rates

Chemotherapy	Study	Treatment Group	N *	% with Complete Response	p-value *
Moderately Emetogenic	1	AlOXI 0.25 mg	189	81	0.009
		Ondansetron 32 mg I.V.	185	69	
	2	AlOXI 0.25 mg	189	83	NS
		Dolasetron 100 mg I.V.	191	63	
Highly Emetogenic	3	AlOXI 0.25 mg	223	59	NS
		Ondansetron 32 mg I.V.	221	57	

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

Chemotherapy	Study	Treatment Group	N *	% with Complete Response	p-value *
Moderately Emetogenic	1	AlOXI 0.25 mg	189	74	<0.001
		Ondansetron 32 mg I.V.	185	55	
	2	AlOXI 0.25 mg	189	54	0.004
		Dolasetron 100 mg I.V.	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 6: Prevention of Overall Nausea and Vomiting (0-120 hours): Complete Response Rates

Chemotherapy	Study	Treatment Group	N *	% with Complete Response	p-value *
Moderately Emetogenic	1	AlOXI 0.25 mg	189	69	<0.001
		Ondansetron 32 mg I.V.	185	50	
	2	AlOXI 0.25 mg	189	46	0.021
		Dolasetron 100 mg I.V.	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.

Chemotherapy-Induced Nausea and Vomiting in Paediatrics

One double-blind, active-controlled clinical trial was conducted in pediatric cancer patients. The total population (N = 327) had a mean age of 8.3 years (range 2 months to 16.9 years) and were 53% male; and 96% white. Patients were randomized and received a 20 mcg/kg (maximum 1.5 mg) intravenous infusion of ALOXI 30 minutes prior to the start of emetogenic chemotherapy (followed by placebo infusions 4 and 8 hours after the dose of palonosetron) or 0.15 mg/kg of intravenous ondansetron 30 minutes prior to the start of emetogenic chemotherapy (followed by ondansetron 0.15 mg/kg infusions 4 and 8 hours after the first dose of ondansetron, with a maximum total dose of 32 mg). Emetogenic chemotherapies administered included doxorubicin, cyclophosphamide (<1500 mg/m²), ifosfamide, cisplatin, dactinomycin, carboplatin, and daunorubicin. Adjuvant corticosteroids, including dexamethasone, were administered with chemotherapy in 55% of patients.

Complete Response in the acute phase of the first cycle of chemotherapy was defined as no vomiting, no retching, and no rescue medication in the first 24 hours after starting chemotherapy. Efficacy was based on demonstrating non-inferiority of intravenous

palonosetron compared to intravenous ondansetron. Non-inferiority criteria were met if the lower bound of the 97.5% confidence interval for the difference in Complete Response rates of intravenous palonosetron minus intravenous ondansetron was larger than -15%. The non-inferiority margin was 15%.

Efficacy Results

As shown in Table 7, intravenous ALOXI 20 mcg/kg (maximum 1.5 mg) demonstrated non-inferiority to the active comparator during the 0 to 24 hour time interval.

Table 7: Prevention of Acute Nausea and Vomiting (0-24 hours): Complete Response Rates

I.V. ALOXI 20 mcg/kg (N=165)	I.V. Ondansetron 0.15 mg/kg x 3 (N=162)	Difference [97.5% Confidence Interval]: I.V. ALOXI minus I.V. Ondansetron Comparator
59.4%	58.6%	0.36% [-11.7%, 12.4%]

* To adjust for multiplicity of treatment groups, a lower-bound of a 97.5% confidence interval was used to compare to -15%, the negative value of the non-inferiority margin.

In patients that received ALOXI at a lower dose than the recommended dose of 20 mcg/kg, non-inferiority criteria were not met.

Postoperative Nausea and Vomiting

In one multicenter, randomized, stratified, double-blind, parallel-group, phase 3 clinical study (Study 1), palonosetron was compared with placebo for the prevention of PONV in 546 patients undergoing abdominal and gynecological surgery. All patients received general anesthesia. Study 1 was a pivotal study conducted predominantly in the US in the out-patient setting for patients undergoing elective gynecologic or abdominal laparoscopic surgery and stratified at randomization for the following risk factors: gender, non-smoking status, history of post-operative nausea and vomiting and/or motion sickness.

In Study 1 patients were randomized to receive palonosetron 0.025 mg, 0.050 mg or 0.075 mg or placebo, each given intravenously immediately prior to induction of anesthesia. The antiemetic activity of palonosetron was evaluated during the 0 to 72 hour time period after surgery.

Of the 138 patients treated with 0.075 mg palonosetron in Study 1 and evaluated for efficacy, 96% were women; 66% had a history of PONV or motion sickness; 85% were non-smokers. As for race, 63% were White, 20% were Black, 15% were Hispanic, and 1% were Asian. The age of patients ranged from 21 to 74 years, with a mean age of 37.9 years. Three patients were greater than 65 years of age.

Co-primary efficacy measures were Complete Response (CR) defined as no emetic episode and no use of rescue medication in the 0-24 and in the 24-72 hours postoperatively.

- Secondary efficacy endpoints included:
- Complete Response (CR) 0-46 and 0-72 hours
 - Complete Control (CC) defined as CR and no more than mild nausea
 - Severity of nausea (none, mild, moderate, severe)

The primary hypothesis in Study 1 was that at least one of the three palonosetron doses were superior to placebo.

Results for Complete Response in Study 1 for 0.075 mg palonosetron versus placebo are described in the following table.

Table 8: Prevention of Postoperative Nausea and Vomiting: Complete Response (CR), Study 1, Palonosetron 0.075 mg Vs Placebo

Treatment	n/N (%)	Palonosetron Vs Placebo	
		Δ	p-value*
Co-primary Endpoints			
CR 0-24 hours			
Palonosetron	59/138 (42.8%)	16.8%	0.004
Placebo	35/135 (25.9%)		
CR 24-72 hours			
Palonosetron	67/138 (48.6%)	7.8%	0.188
Placebo	55/135 (40.7%)		

* To reach statistical significance for each co-primary endpoint, the required significance limit for the lowest p-value was p<0.017.
Δ Difference (%): palonosetron 0.075 mg minus placebo

Palonosetron 0.075 mg reduced the severity of nausea compared to placebo. Analyses of other secondary endpoints indicate that palonosetron 0.075 mg was numerically better than placebo, however, statistical significance was not formally demonstrated.

A phase 2 randomized, double-blind, multicenter, placebo-controlled, dose ranging study was performed to evaluate I.V. palonosetron for the prevention of post-operative nausea and vomiting following abdominal or vaginal hysterectomy. Five I.V. palonosetron doses (0.1, 0.3, 1.0, 3.0 and 30 µg/kg) were evaluated in a total of 381 intent-to-treat patients. The primary efficacy measure was the proportion of patients with CR in the first 24 hours after recovery from surgery. The lowest effective dose was palonosetron 1 µg/kg (approximately 0.075 mg) which had a CR rate of 44% versus 19% for placebo, p=0.004. Palonosetron 1 µg/kg also significantly reduced the severity of nausea versus placebo, p=0.009.

PHARMACEUTICAL PARTICULARS

List of excipients

Mannitol
Disodium edetate
Sodium citrate
Citric acid monohydrate
Sodium hydroxide (for pH adjustment)
Hydrochloric acid (for pH adjustment)
Water for injections

Incompatibilities

This medicinal product must not be mixed with other medicinal products.

Shelf life

5 years
Upon opening of the vial, use immediately and discard any unused solution.

Special precautions for storage

Protect from light.
Store below 30°C.

STORE OUT OF THE REACH OF CHILDREN

Nature and contents of container

Type I glass vial with chlorobutyl siliconised rubber stopper and aluminium cap.
Available as:

ALOXI Injection 0.25 mg/ 5 ml single use vial individually packaged in a carton

ALOXI Injection 0.075 mg/ 1.5 ml single use vial packaged in a carton containing 5 vials.

Special precautions for disposal

Single use only, any unused solution should be discarded.
Any unused product or waste material should be disposed of in accordance with local requirements.

MANUFACTURER

Fareva Pau
Fareva Pau 1
Avenue de Béarn
64320 IDRON
France

PRODUCT REGISTRATION HOLDER

Juniper Biologics Sdn. Bhd.
12th Floor, Menara Symphony,
No. 5, Jalan Prof. Khoo Kay Kim, Seksyen 13,
46200 Petaling Jaya,
Selangor, Malaysia.

Under licence of Helsinn Healthcare SA, Switzerland.

DATE OF REVISION OF THE TEXT

August 2023 (based on US FDA PI version Sept 2014)

ALOXI is a Registered Trademark used by Juniper Biologics as Authorised User.

*PMS Colours to be listed on each film (beside or on top of the Proof Image)

Tel: + 353 (0) 1 822 5404		HELSINN BIREX PHARMACEUTICALS LTD		Darnastown,	
Fax: + 353 (0) 1 822 5410				Mulhuddart, Dublin 15	
Customer :	Helsinn Birex	Customer Approval :	Sumitha	Date :	13 Apr 2024
HBPItem :	# 0201204036	# of colours :	1	HBPApproval :	Date :
Proof :	# 3	Proof Date :	05-04-2024	Proofed by :	TRACY
Printer Part :	# 00171433	Varnish free area :	N/A	Verified by :	Date :
Design Description :	MAL Juniper ALOXI PONV PIL	Cutter Ref # :		Die Size :	
TS :	# 153	Reel Width :	N/A	Design Repeat :	N/A
Pharmacode :	# 2712	Glue Flap # :	N/A	Barcode # :	N/A
Pantone Matching System (PMS Colours) :	Black	Font Size :	Supplied File	Unwind Direction :	N/A
ESSENTIA PACKAGING IRELAND,	IDA INDUSTRIAL ESTATE, OVENS, CO. CORK	PO # :	24000258		
TEL: +353 21 4805 600 FAX: +353 21 485 0649		Printer # :	N/A		

Please check proof carefully, while every effort has been taken to ensure it is correct, when you are satisfied please sign above and return.