

1. NAME OF THE MEDICINAL PRODUCT

Aloxi 0.25 mg per 5 ml Solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Palonosetron 0.25 mg (as hydrochloride) in 5 ml of solution, 0.05 mg/ml (For excipients, see 6.1)

3. PHARMACEUTICAL FORM

Solution for injection. Clear, colourless solution.

4. CLINICAL PARTICULARS**4.1 Therapeutic indications**

Aloxi injection is indicated for: the prevention of acute nausea and vomiting associated with highly emetogenic cancer chemotherapy and the prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy.

4.2 Posology and method of administration (For intravenous use)**Adults:**

0.25 mg, administered as a single intravenous bolus approximately 30 minutes before the start of each chemotherapy. Aloxi should be injected over 30 seconds.

Repeated dosing of Aloxi within a seven day interval is not recommended.

The efficacy of Aloxi 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.

Elderly:

No dosage adjustment is necessary.

Children and adolescents:

Use in patients under 18 years of age is not recommended until further data become available.

Special populations:

Dose adjustment is not required in patients with impaired renal or hepatic function.

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

4.3 Contraindications

Hypersensitivity to palonosetron or to any of the excipients.

4.4 Special warnings and special precautions for use

As palonosetron may increase large bowel transit time, patients with a history of constipation or signs of subacute intestinal obstruction should be monitored following administration. Two cases of constipation with faecal impaction requiring hospitalisation have been reported in association with palonosetron 750 micrograms.

At all dose levels tested, palonosetron did not induce clinically relevant prolongation of the QTc interval. However, as for other 5-HT₃ 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.

4.5 Interaction with other medicinal products and other forms of interaction

In preclinical studies, palonosetron did not inhibit the antitumour activity of the five chemotherapeutic agents tested (cisplatin, cyclophosphamide, cytarabine, doxorubicin and mitomycin C). In clinical studies no significant pharmacokinetic interaction was shown between a single intravenous dose of palonosetron and steady state oral metoclopramide. It has been shown that there was no significant effect on palonosetron clearance of co-medication with CYP2D6 inducers (dexamethasone and rifampicin) and inhibitors (including amiodarone, celecoxib, chlorpromazine, cimetidine, doxorubicin, fluoxetine, haloperidol, paroxetine, quinidine, ranitidine, ritonavir, sertraline or terbinafine).

Palonosetron has been administered safely with corticosteroids, analgesics, antiemetic/antinauseants, antispasmodics and anticholinergic agents.

4.6 Pregnancy and lactation

For Aloxi, no clinical data on exposed pregnancies are available.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see 5.3).

Caution should be exercised when prescribing to pregnant women.

It is not known whether Aloxi is excreted in human milk.

4.7 Effects on ability to drive and use machines

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

Patients who develop dizziness, somnolence or fatigue should be cautioned to avoid driving or operating machinery.

4.8 Undesirable effects

In clinical studies at a dose of 0.25 mg (in a total of 633 patients) the majority of adverse events, at least possibly related to Aloxi, were headache (9%) & constipation (5%).

In the clinical studies the following adverse events were reported as possibly or probably related to Aloxi. These were classified as common (between 1% and 10% of patients) or uncommon (between 0.1% and 1% of patients).

System Organ Class	Common AEs (>1/100 to <1/10)	Uncommon AEs (>1/1,000 to <1/100)
Metabolism and nutrition disorders		Hyperkalaemia, metabolic disorders, hypocalcaemia, anorexia, hyperglycaemia, appetite decreased
Psychiatric disorders		Anxiety, euphoric mood
Nervous system disorders	Headache, Dizziness	Somnolence, insomnia, paraesthesia, hypersomnia, peripheral sensory neuropathy
Eye disorders		Eye irritation, amblyopia
Ear and labyrinth disorders		Motion sickness, tinnitus
Cardiac disorders		Tachycardia, bradycardia, extrasystoles, myocardial ischaemia, sinus tachycardia, sinus arrhythmia, upraventricular extrasystoles
Vascular disorders		Hypotension, hypertension, vein discoloration, vein distended
Respiratory, thoracic and mediastinal disorders		Hiccups
Gastrointestinal disorders	Constipation, Diarrhoea	Dyspepsia, abdominal pain, upper abdominal pain, dry mouth, flatulence
Hepato-biliary disorders		Hyperbilirubinaemia
Skin and subcutaneous tissue disorders		Dermatitis allergic, rash pruritic
Musculoskeletal and connective tissue disorders		Arthralgia
Renal and urinary disorders		Urinary retention, glycosuria
General disorders and administration site conditions		Asthenia, pyrexia, fatigue, feeling hot, influenza like illness
Investigations		Elevated transaminases, hypokalaemia, electrocardiogram QT prolonged

4.9 Overdose

No case of overdose has been reported.

Doses of up to 6 mg have been used in clinical trials, with a similar incidence of adverse events being observed as at 0.25 mg. No dose response effects were observed. In the unlikely event of overdose with Aloxi, this should be managed with supportive care. Dialysis studies have not been performed, however, due to the large volume of distribution, dialysis is unlikely to be an effective treatment for Aloxi overdose.

5. PHARMACOLOGICAL PROPERTIES**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Antiemetics and antinauseants, serotonin (5HT₃) antagonists.

Palonosetron is a selective high-affinity receptor antagonist of the 5HT₃ receptor.

In two randomised, double-blind studies with a total of 1,132 patients receiving moderately emetogenic chemotherapy that included cisplatin ≤ 50mg/m², carboplatin, cyclophosphamide ≤ 1,500 mg/m² and doxorubicin > 25mg/m², palonosetron 250 micrograms and 750 micrograms were compared with ondansetron 32 mg (half-life 4 hours) or dolasetron 100 mg (half-life 7.3 hours) administered intravenously on Day 1, without dexamethasone.

In a randomised, double-blind study with a total of 667 patients receiving highly emetogenic chemotherapy that included cisplatin ≥ 60mg/m², cyclophosphamide > 1,500 mg/m² and dacarbazine, palonosetron 250 micrograms and 750 micrograms were compared with ondansetron 32 mg administered intravenously on Day 1. Dexamethasone was administered prophylactically before chemotherapy in 67% of patients.

The pivotal studies were not designed to assess efficacy of palonosetron in delayed onset nausea and vomiting. The antiemetic activity was observed during 0-24, 24-120 and 0-120 hours. Results for the studies on moderately emetogenic chemotherapy and for the study on highly emetogenic chemotherapy are summarised in the following tables.

Palonosetron was non-inferior versus the comparators in the acute phase of emesis both in moderately and highly emetogenic setting.

Although comparative efficacy of palonosetron in multiple cycles has not been demonstrated in controlled clinical trials, 875 patients enrolled in three phase 3 trials continued in an open label safety study and were treated with palonosetron 750 mg for up to 9 additional cycles of chemotherapy. The overall safety was maintained during all cycles.

Table 1: Percentage of patients^a responding by treatment group and phase in the Moderately Emetogenic Chemotherapy study versus ondansetron

	Aloxi (250 micrograms) (n = 189) %	Ondansetron (32 milligrams) (n = 185) %	Delta %	
Complete Response (No Emesis and No Rescue Medication)				97.5% CI^b
0 – 24 hours	81.0	68.6	12.4	[1.8%, 22.8%]
24 – 120 hours	74.1	55.1	19.0	[7.5%, 30.3%]
0 – 120 hours	69.3	50.3	19.0	[7.4%, 30.7%]
Complete Control (Complete Response and No More Than Mild Nausea)				p-value^c
0 – 24 hours	76.2	65.4	10.8	NS
24 – 120 hours	66.7	50.3	16.4	0.001
0 – 120 hours	63.0	44.9	18.1	0.001
No Nausea (Likert Scale)				p-value^c
0 – 24 hours	60.3	56.8	3.5	NS
24 – 120 hours	51.9	39.5	12.4	NS
0 – 120 hours	45.0	36.2	8.8	NS

^a Intent-to-treat cohort. The study was designed to show non-inferiority. A lower bound greater than —15% demonstrates non-inferiority between Aloxi and comparator. Chi-square test. Significance level at $\alpha=0.05$.

Table 2: Percentage of patients^a responding by treatment group and phase in the Moderately Emetogenic Chemotherapy study versus dolasetron

	Aloxi (250 micrograms) (n = 185) %	Dolasetron (100 milligrams) (n = 191) %	Delta %	
Complete Response (No Emesis and No Rescue Medication)				97.5% CI^b
0 – 24 hours	63.0	52.9	10.1	[-1.7%, 21.9%]
24 – 120 hours	54.0	38.7	15.3	[3.4%, 27.1%]
0 – 120 hours	46.0	34.0	12.0	[0.3%, 23.7%]
Complete Control (Complete Response and No More Than Mild Nausea)				p-value^c
0 – 24 hours	57.1	47.6	9.5	NS
24 – 120 hours	48.1	36.1	12.0	0.018
0 – 120 hours	41.8	30.9	10.9	0.027
No Nausea (Likert Scale)				p-value^c
0 – 24 hours	48.7	41.4	7.3	NS
24 – 120 hours	41.8	26.2	15.6	0.001
0 – 120 hours	33.9	22.5	11.4	0.014

^a Intent-to-treat cohort. The study was designed to show non-inferiority. A lower bound greater than —15% demonstrates non-inferiority between Aloxi and comparator. Chi-square test. Significance level at $\alpha=0.05$.

Table 3: Percentage of patients^a responding by treatment group and phase in the Highly Emetogenic Chemotherapy study versus ondansetron

	Aloxi (250 micrograms) (n = 223) %	Ondansetron (32 milligrams) (n = 221) %	Delta %	
Complete Response (No Emesis and No Rescue Medication)				97.5% CI^b
0 – 24 hours	59.2	57.0	2.2	[-8.8%, 13.1%]
24 – 120 hours	45.3	38.9	6.4	[-4.6%, 17.3%]
0 – 120 hours	40.8	33.0	7.8	[-2.9%, 18.5%]
Complete Control (Complete Response and No More Than Mild Nausea)				p-value^c
0 – 24 hours	56.5	51.6	4.9	NS
24 – 120 hours	40.8	35.3	5.5	NS
0 – 120 hours	37.7	29.0	8.7	NS
No Nausea (Likert Scale)				p-value^c
0 – 24 hours	53.8	49.3	4.5	NS
24 – 120 hours	35.4	32.1	3.3	NS
0 – 120 hours	33.6	32.1	1.5	NS

^a Intent-to-treat cohort. The study was designed to show non-inferiority. A lower bound greater than —15% demonstrates non-inferiority between Aloxi and comparator. Chi-square test. Significance level at $\alpha=0.05$.

5.2 Distribution

Palonosetron at the recommended dose is widely distributed in the body with a volume of distribution of approximately 6.9 to 7.9 L/kg. Approximately 62% of Palonosetron is bound to plasma proteins.

Metabolism

Palonosetron is eliminated by dual route, about 40 % eliminated through the kidney and with approximately 50% metabolised to form two primary metabolites, which have less than 1% of the 5-HT₃ receptor antagonist activity of palonosetron. *In vitro* metabolism studies have shown 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 metabolisers of CYP2D6 substrates. Palonosetron does not inhibit or induce cytochrome P450 isozymes at clinically relevant concentrations.

Elimination

After a single intravenous dose of 10 µg/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, as unchanged drug. After a single intravenous bolus administration in healthy subjects the total body clearance of palonosetron was 173 ± 73 ml/min and renal clearance was 53 ± 29 ml/min. The low total body clearance and large volume of distribution resulted in a terminal elimination half-life in plasma of approximately 40 hours. Ten percent of patients have a mean terminal elimination half-life greater than 100 hours.

Pharmacokinetics in special populations

Elderly: age does not affect the pharmacokinetic of palonosetron. No dosage adjustment is necessary in elderly patients.

Gender: gender does not affect the pharmacokinetics of palonosetron. No dosage adjustment is necessary based on gender.

Paediatric patients: no pharmacokinetic data are available in patients below 18 years of age.

Renal impairment: mild to moderate renal impairment does not significantly affect palonosetron pharmacokinetic parameters. Severe renal impairment reduces renal clearance, however total body clearance in these patients is similar to healthy subjects. No dosage adjustment is necessary in patients with renal insufficiency. No pharmacokinetic data in haemodialysis patients are available.

Hepatic impairment: hepatic impairment does not significantly affect total body clearance of palonosetron compared to the healthy subjects. While the terminal elimination half-life and mean systemic exposure of palonosetron is increased in the subjects with severe hepatic impairment, this does not warrant dose reduction.

5.3 Preclinical safety data

Preclinical effects were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients: Mannitol, Disodium edentate, Sodium citrate, Citric acid monohydrate, Water for injections, pH adjusted to 5.0 ± 0.5 with 1N sodium hydroxide solution and/or 1N hydrochloric acid solution.

6.2 Incompatibilities

In the absence of compatibility studies, Aloxi must not be mixed with other medicinal products.

6.3 Shelf life

3 years. Upon opening of the vial, any unused solution should be discarded.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original container. Keep container in the outer carton in order to protect from light.

6.5 Nature and contents of container

Type I flint glass vial with chlorobutyl siliconised rubber stopper and flip off seal. Available in packs of 1 vial.

6.6 Instructions for use and handling

From a microbiological point of view, unless the method of opening precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

7. MANUFACTURER

Pierre-Fabre Medicament production, Aquitaine Pharm Internationa, Avenue de Bearn, 64320 Idron, France

Mfd for Helsinn Healthcare SA, Switzerland

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