Aloxi®
palonosetron HCl injection

STARTS STRONG LASTS LONG

EVOLUTION
IN EMESIS CONTROL

Single 0.25mg fixed IV dose

Fannin

Presentation: A vial of 5 ml of clear, colourless solution contains 250 micrograms palonosetron (as hydrochloride). **Indications:** 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 in adults. **Posology and method of administration:** *Adults:* 250 micrograms palonosetron administered as a single intravenous bolus approximately 30 minutes before the start of chemotherapy. Aloxi should be injected over 30 seconds. 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 dose adjustment is necessary for the elderly. ***Children (under 18 years of age):*** The safety and efficacy in children have not been established. *Currently clinical data are available in paediatric population treated for the prevention of Chemotherapy Induced Nausea and Vomiting (CINV) and Prevention of Post Operative Nausea and Vomiting (PONV), as described in detail here-after. However, no recommendation on posology can be made.* **CINIV** - The safety and efficacy of Palonosetron i.v at single doses of 3µg/kg and 10µg/kg was investigated in a clinical study in 72 patients in the following age groups, >28 days to 23 months (12 patients), 2 to 11 years (31 patients), and 12 to 17 years of age (29 patients), receiving highly or moderately emetogenic chemotherapy. No safety concerns were raised at either dose level. The primary efficacy variable was the proportion of patients with a complete response (CR, defined as no emetic episode and no rescue medication) during the first 24 hours after the start of chemotherapy administration. Efficacy after palonosetron 10 µg/kg compared to palonosetron 3µg/kg was 54.1% and 37.1% respectively. **PONV** - The safety and efficacy of Palonosetron i.v at single doses of 1µg/kg and 3µg/kg was compared in a clinical study in 150 patients in the following age groups, >28 days to 23 months (7 patients), 2 to 11 years (96 patients), and 12 to 16 years of age (47 patients) undergoing elective surgery. No safety concerns were raised in either treatment group. The proportion of patients without emesis during 0-72 hours post-operatively was similar after palonosetron 1 µg/kg or 3 µg/kg (88% vs 84%)

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. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. **Special Warnings and 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. A specific thorough QT/QTc study was conducted in healthy volunteers for definitive data demonstrating the effect of palonosetron on QT/QTc. However, as for 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. Aloxi should not be used to prevent or treat nausea and vomiting in the days following chemotherapy if not associated with another chemotherapy administration. This medicinal product contains less than 1 mmol sodium (23 mg) per vial, i.e. essentially 'sodium-free'. **Interaction with other medicinal products and other forms of interaction:** Please refer to the full text of the summary of product characteristics.

Fertility, pregnancy and lactation: There is no experience of palonosetron in human pregnancy. Therefore, palonosetron should not be used in pregnant women unless it is considered essential by the physician. There are no data concerning palonosetron excretion in breast milk, breast-feeding should be discontinued during therapy. There are no data concerning the effect of palonosetron on fertility.

Effects on ability to drive and use machines: No studies on the effects on the ability to drive and use machines have been performed. Since palonosetron may induce dizziness, somnolence or fatigue, patients should be cautioned when driving or operating machines.

Undesirable effects: In clinical studies at a dose of 250 micrograms (total 633 patients) the most frequently observed adverse reactions, at least possibly related to Aloxi, were headache (9 %) and constipation (5 %).These are classified as *common (≥1/100 to <1/10) or uncommon (≥1/1,000 to <1/100). Very rare (<1/10,000) adverse reactions were reported post-marketing.* - **Common ARs:** Headache, Dizziness, Constipation, Diarrhoea - **Uncommon ARs:** Hyperkalaemia, metabolic disorders, hypocalcaemia, hypokalaemia, anorexia, hyperglycaemia, appetite decreased, anxiety, euphoric mood, somnolence, insomnia, paraesthesia, hypersomnia, peripheral sensory neuropathy, eye irritation, amblyopia, motion sickness, tinnitus, tachycardia, bradycardia, extrasystoles, myocardial ischaemia, sinus tachycardia, sinus arrhythmia, supraventricular extrasystoles, hypotension, hypertension, vein discolouration, vein distended, hiccups, dyspepsia, abdominal pain, abdominal pain upper, dry mouth, flatulence, hyperbilirubinaemia, dermatitis allergic, pruritic rash, arthralgia, urinary retention, glycosuria, asthenia, pyrexia, fatigue, feeling hot, influenza like illness, elevated transaminases-, electrocardiogram QT prolonged- **Very rare ARs:** Hypersensitivity, injection site reaction (burning, induration, discomfort and pain)

Pharmacodynamic properties: Palonosetron is a selective high-affinity receptor antagonist of the 5HT$_3$ receptor. In two randomised, double-blind studies with a total of 1,132 patients receiving moderately emetogenic chemotherapy that included cisplatin ≤50 mg/m^2, carboplatin, cyclophosphamide d1,500 mg/m^2 and doxorubicin >25 mg/m^2, 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 ≥ 60 mg/m^2, cyclophosphamide > 1,500 mg/m^2 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 hours, 24 120 hours 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 studies, 875 patients enrolled in the three phase 3 trials continued in an open label safety study and were treated with palonosetron 750 micrograms for up to 9 additional cycles of chemotherapy. The overall safety was maintained during all cycles.

References:

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.
[b] The study was designed to show non-inferiority. A lower bound greater than –15 % demonstrates non-inferiority between Aloxi and comparator.
[c] Chi-square test. Significance level at α=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.
[b] The study was designed to show non-inferiority. A lower bound greater than –15 % demonstrates non-inferiority between Aloxi and comparator.
[c] Chi-square test. Significance level at α=0.05.

Package Quantity: Available in packs of 1 vial containing 5ml solution. **MA Holder:** Helsinn Birex Pharmaceuticals Ltd., Damastown, Mulhuddart, Dublin 15, Republin of Ireland. **MA Number:** EU/1/04/306/001.
Date of revision of text: December 2010

Medical product subject to medical prescription

FN2012/05/009

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SUMMARY OF THE EUROPEAN SmPC

Full prescribing information available upon request from:
Fannin House, South County Business Park, Leopardstown, Dublin 18
Tel:01 290 7000 Fax:01 290 7111 Email: medinfo@fannin.ie

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