ALOXI®
Palonosetron HCl injection.
Injection solution.

COMPOSITION
Each ALOXI vial of solution contains:
Active ingredient: 0.25 mg palonosetron (Equivalent to 0.28 mg palonosetron hydrochloride)
Excipients: Mannitol, Disodium edetate, Sodium citrate, Citric acid, Sodium hydroxide (for pH adjustment) Water q.s to 5ml. PH of solution is 4.5-5.5.

PHARMACODYNAMICS
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.

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 (Cmax) and area under the concentration-time curve (AUC0-∞) 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•hr/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 $8.3 \pm 2.5$ 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, CYP3A4 and CYP1A2 are involved in the metabolism of palonosetron.

**Elimination**

After a single intravenous dose of 10 mcg/kg $[^{14}\text{C}]$-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 $160 \pm 35$ mL/h/kg and renal clearance was $66.5 \pm 18.2$ mL/h/kg. Mean terminal elimination half-life is approximately 40 hours.

**INDICATIONS**

**Chemotherapy-Induced Nausea and Vomiting**

ALOXI is indicated for:

- Moderately emetogenic cancer chemotherapy -- prevention of acute and delayed nausea and vomiting associated with initial and repeat courses
- Highly emetogenic cancer chemotherapy -- prevention of acute and delayed nausea and vomiting associated with initial and repeat courses

**Postoperative Nausea and Vomiting**

ALOXI is indicated for:

- 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, ALOXI is recommended even where the incidence of postoperative nausea and/or vomiting is low.

**CONTRAINDICATIONS**

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

Children: No use for children under 18 years old.
DOSAGE AND ADMINISTRATION

Recommended Dosing

Chemotherapy-Induced Nausea and Vomiting

Dosage for Adults – a single 0.25 mg I.V. dose administered over 30 seconds. Dosing should occur approximately 30 minutes before the start of chemotherapy.

Postoperative Nausea and Vomiting

Dosage for Adults - a single 0.075 mg I.V. dose administered over 10 seconds immediately before the induction of anesthesia.

Instructions for I.V. Administration

ALOXI is supplied ready for intravenous injection. ALOXI should not be mixed with other drugs. Flush the infusion line with normal saline before and after administration of ALOXI.

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

WARNINGS AND PRECAUTIONS

Hypersensitivity: Hypersensitive reactions can occur in patients with a history of being hypersensitive with 5-HT₃ receptor antagonist.

QTc interval: Although palonosetron is safely administered for 192 patients accompanied by heart failure in phase 3 study. Aloxi should be used with caution for patients who have or are likely to develop prolongation of cardiac conduction, particularly prolongation of the QTc interval. Caution should be also exercised in patients with hypokalemia and hypomagnesemia congenital, patients taking diuretics that probably causes electrolyte disturbances, patients with congenital QT syndrome, patients taking anti-arrhythmic agents or other medicinal products that lead to QT prolongation and patients treated with anthracycline accumulatively high dose.

In three crucial studies, ECG before and 24 hours after taking palonosetron or a comparative medicine. The rate of patients who change QT and QTc intervals (absolute value > 500 msec or change > 60 msec compared to initiation) is equivalent to comparative drug.

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.

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**

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 Aloxi 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, Aloxi efficacy in geriatric patients has not been adequately evaluated.

**Renal Impairment**

Mild to moderate renal impairment does not significantly affect palonosetron pharmacokinetic parameters. 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.

**Pre-clinical Study**

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.

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.

Palonosetron was not genotoxic in the Ames test. However, palonosetron also cause gene mutation in CHO cell 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.

**EFFECT ON DRIVE AND USING MACHINES ABILITY**

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.

**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.

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, Cmax: 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, 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.

**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 mcg/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.

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

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 1).

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

<table>
<thead>
<tr>
<th>Event</th>
<th>ALOXI 0.25 mg (N=633)</th>
<th>Ondansetron 32 mg I.V. (N=410)</th>
<th>Dolasetron 100 mg I.V. (N=194)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>60 (9%)</td>
<td>34 (8%)</td>
<td>32 (16%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>29 (5%)</td>
<td>8 (2%)</td>
<td>12 (6%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8 (1%)</td>
<td>7 (2%)</td>
<td>4 (2%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>8 (1%)</td>
<td>9 (2%)</td>
<td>4 (2%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 (&lt; 1%)</td>
<td>4 (1%)</td>
<td>4 (2%)</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>1 (&lt; 1%)</td>
<td>2 (&lt; 1%)</td>
<td>3 (2%)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>1 (&lt; 1%)</td>
<td>3 (1%)</td>
<td>3 (2%)</td>
</tr>
</tbody>
</table>

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 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, paresthesia.

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

Urinary System: < 1%: urinary retention.

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

**Postoperative Nausea and Vomiting**

The adverse reactions cited in Table 2 were reported in ≥ 2% of adults receiving I.V. Aloxi 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.

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

<table>
<thead>
<tr>
<th>Event</th>
<th>Aloxi 0.075 mg (N=336)</th>
<th>Placebo (N=369)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electrocardiogram QT prolongation</td>
<td>16 (5%)</td>
<td>11 (3%)</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>13 (4%)</td>
<td>16 (4%)</td>
</tr>
<tr>
<td>Headache</td>
<td>11 (3%)</td>
<td>14 (4%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>8 (2%)</td>
<td>11(3%)</td>
</tr>
</tbody>
</table>

In these 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 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 postapproval use of ALOXI. 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 including anaphylaxis and anaphylactic shock and injection site reactions (burning, induration, discomfort and pain) were reported from postmarketing experience of ALOXI 0.25 mg in the prevention of chemotherapy-induced nausea and vomiting.

*Please inform your doctor if you have any undesirable effects occurring when using this drug.*

PACKING AND STORAGE CONDITIONS

Aloxi injection 0.25mg/5ml, Box of 1 bottle. NDC#58063-797-25

Store at room temperature from 20-25°C. Protect from light.

*Keep out of reach of children. Not using drug when exceeding the expiry date stated on the label.*

SELF LIFE: 60 months from manufacture date

SPECIFICATION: Manufacture’s

MANUFACTURER

HELSINN BIREX PHARMACEUTICALS LTD.

Damastown, Mulhuddart, Dublin 15, Ireland.