PRODUCT MONOGRAPH

PrALOXI®

(palonosetron injection)
as palonosetron hydrochloride

0.05 mg/mL palonosetron

PrALOXI®

(palonosetron capsules)
as palonosetron hydrochloride

0.5 mg palonosetron

Anti-emetic (5-HT_3 receptor antagonist)

A04AA05

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ALOXI®
palonosetron hydrochloride

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Non-medicinal Ingredients
Intravenous	Solution for injection: 0.25 mg palonosetron (as palonosetron hydrochloride)/5 mL (0.05 mg/mL)	Citrate buffer in water, disodium edetate, and mannitol.
Oral	Capsule: 0.5 mg palonosetron (as palonosetron hydrochloride)	Black printing ink, butylated hydroxyanisole, gelatin, glycerin, monoglycerides and diglycerides of capryl/capric acid, polyglyceryl oleate, sorbitol, titanium dioxide, water. May contain traces of medium chain triglyceride and lecithin.

INDICATIONS AND CLINICAL USE

ALOXI injection is indicated in adults for:

- the prevention of acute and delayed nausea and vomiting associated with moderately emetogenic cancer chemotherapy
- the prevention of acute nausea and vomiting associated with highly emetogenic cancer chemotherapy, including high dose cisplatin

ALOXI capsules are indicated in adults for:

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

Geriatrics (≥ 65 years of age):
No overall differences in safety or effectiveness were observed between patients ≥ 65 years of age and younger patients (18 to 64 years).

Pediatrics (< 18 years of age):
Safety and effectiveness in patients below the age of 18 years have not been established.

CONTRAINDICATIONS

ALOXI (palonosetron hydrochloride) is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.

WARNINGS AND PRECAUTIONS

Carcinogenesis and Mutagenesis
Statistically significant increased incidences of a variety of different tumors affecting the adrenal, liver, mammary gland, and other tissues and organs were observed at high doses of palonosetron in a rat carcinogenicity study. In the mouse study the findings were not attributed to palonosetron treatment (see TOXICOLOGY/Carcinogenicity). Experimental evidence indicates that palonosetron is non-mutagenic (see TOXICOLOGY/Genotoxicity).

Cardiac/QTc prolongation
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 (see DETAILED PHARMACOLOGY). At all dose levels tested in the CINV pivotal clinical studies, cases of QTc prolongation were reported in the ALOXI treatment groups, although those cases were not considered clinically significant (see ADVERSE REACTIONS/Less Common Clinical Trial Adverse Reactions).

A thorough QT/QTc study with moxifloxacin as a positive control demonstrated a dose-dependent increase from baseline in maximum QTcI interval and increased numbers of patients with QTcI change of 30-60 msec in three palonosetron dose groups although the effect at doses up to 2.25 mg was below that of moxifloxacin. No clinically significant changes were shown on heart rate, atrioventricular (AV) conduction and cardiac repolarization (see ACTION AND CLINICAL PHARMACOLOGY/Pharmacodynamics).

Caution should be exercised in the concomitant use of ALOXI with medicinal products that increase the QT interval or in patients who have or are likely to develop prolongation of QT interval (e.g. congenital QT Syndrome, electrolyte imbalance).

Hepatic
Hepatic impairment does not significantly affect total body clearance of intravenous palonosetron compared to the healthy subjects. However, the terminal half-lives of palonosetron were increased in patients with moderate and severe degrees of hepatic impairment (see ACTION AND CLINICAL PHARMACOLOGY/Special Populations and Conditions/Hepatic Insufficiency). Dosage adjustment is not necessary in patients with any degree of hepatic impairment.

Renal
Mild to moderate renal impairment does not significantly affect palonosetron pharmacokinetic parameters. The systemic exposure (AUC_{0-t}) of palonosetron increased by approximately 45% in patients with severe renal impairment relative to healthy subjects. Longer terminal half-lives (estimated 115-300 hours) were also reported in some patients with severe renal impairment (see ACTION AND CLINICAL PHARMACOLOGY/Special Populations and Conditions/Renal Insufficiency). Dosage adjustment is not necessary in patients with mild to severe renal impairment. The pharmacokinetics of palonosetron have not been studied in subjects with end-stage renal disease.

Sensitivity/Resistance
Hypersensitivity reactions may occur in patients who have exhibited hypersensitivity to other 5-HT_3 receptor antagonists. Hypersensitivity reactions have been very rarely reported post-marketing for intravenous palonosetron: dyspnea, bronchospasm, swelling/edema, erythema, pruritus, rash, and urticaria. No hypersensitivity reactions have been reported for oral palonosetron.

Serotonin Syndrome/Neuroleptic Malignant Syndrome-like events
Cases of life-threatening serotonin syndrome or neuroleptic malignant syndrome-like events have been reported with 5-HT_3 receptor antagonist antiemetics, particularly when given in combination with other serotonergic and/or neuroleptic drugs. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

As these syndromes may result in potentially life-threatening conditions, treatment should be discontinued if such events occur and supportive symptomatic treatment should be initiated. If concomitant treatment of ALOXI with a drug affecting the serotonergic neurotransmitter system is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see DRUG INTERACTIONS).

Special Populations

Pregnant Women:
There are 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 Women:
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.

Pediatrics (< 18 years of age):
Safety and effectiveness in patients below the age of 18 years have not been established.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

ALOXI Injection
The most common adverse reactions reported in the 633 patients treated for the prevention of chemotherapy-induced nausea and vomiting with a single dose of 0.25 mg in the ALOXI I.V. pivotal Phase 3 program were headache (9%) and constipation (5%). Dizziness and diarrhea were reported at a rate of 1%.

ALOXI Capsules
Similarly, the most common adverse reactions reported in the 161 patients who received oral palonosetron 0.5 mg were headache (4%) and constipation (0.6%).

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates*.

ALOXI Injection
In clinical trials for the prevention of nausea and vomiting induced by moderately or highly emetogenic chemotherapy, 1374 adult patients received palonosetron, including 633 patients received a single dose of palonosetron 0.25 mg. The duration for monitoring adverse events was 14 days after study drug administration for all patients. Adverse reactions were similar in frequency and severity with ALOXI and ondansetron or dolasetron. Following is a listing of all adverse reactions reported by ≥ 1% of patients in these trials (Table 1). Adverse events known to be caused by chemotherapy such as blood and lymphatic system disorder were not reported as adverse reactions.

Table 1: Adverse Reactions[1] from Chemotherapy-Induced Nausea and Vomiting Studies* with Frequency ≥ 1% in any Treatment Group – ALOXI I.V.

Adverse Reaction[1]	ALOXI 0.25 mg I.V. (N=633)	Ondansetron 32 mg I.V. (N=410)	Dolasetron 100 mg I.V. (N=194)
Any adverse reaction	131 (21%)	77 (19%)	61 (31%)
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%)
Appetite decreased	1 (<1%)	1 (<1%)	2 (1%)
Insomnia	1 (<1%)	3 (<1%)	3 (2%)
Back pain	0 (0%)	1 (<1%)	2 (1%)
Dermatitis	0 (0%)	0 (0%)	2 (1%)

[1] Adverse events assessed by investigators as 'definitively, possibly, or probably' related to study medications.

ALOXI Capsules

In a clinical trial for the prevention of nausea and vomiting induced by moderately emetogenic chemotherapy, a total of 161 adult patients received oral palonosetron 0.5 mg. Following is a listing of drug related adverse reactions reported by ≥ 1% of patients from the clinical trial.

Table 2: Adverse Reactions from the Chemotherapy-Induced Nausea and Vomiting Study*with Frequency ≥ 1% – ALOXI Capsules

Adverse Reaction[1]	0.5 mg oral (N=161)	0.25 mg I.V. (N=163)
Any adverse reaction	13 (8%)	26 (16%)
Headache	6 (4%)	14 (9%)
Constipation	1 (<1%)	5 (3%)

[1] Adverse events assessed by investigators as 'definitively, possibly, or probably' related to study medications.

Less Common Clinical Trial Adverse Drug Reactions (< 1%)

ALOXI Injection

In clinical trials, the following infrequently (< 1%) reported adverse reactions, assessed by investigators as treatment-related or causality unknown, occurred following a single dose of administration of 0.25 mg ALOXI I.V. to adult patients receiving concomitant cancer chemotherapy:

Cardiac Disorders: non-sustained tachycardia, bradycardia, hypotension, myocardial ischemia, extrasystoles, sinus tachycardia, sinus arrhythmia, supraventricular extrasystoles, QT prolongation

Ear and Labyrinth Disorders: motion sickness, tinnitus

Eye Disorders: eye irritation, amblyopia

Gastrointestinal Disorders: dyspepsia, abdominal pain, dry mouth, hiccups, flatulence

General Disorders and Administration Site Conditions: weakness, fatigue, fever, hot flash, flu-like syndrome, asthenia

Hepatobiliary Disorders: transient, asymptomatic increases in AST and/or ALT and bilirubin

Metabolism and Nutrition Disorders: hyperkalemia, hypocalcaemia, electrolyte fluctuations, hyperglycemia, metabolic disorders nos, metabolic acidosis, glycosuria, anorexia

Musculoskeletal and Connective Tissue Disorders: arthralgia

Nervous System Disorders: somnolence, hypersomnia, paresthesia, peripheral sensory neuropathy

Psychiatric Disorders: anxiety, euphoric mood

Renal and Urinary Disorders: urinary retention

Vascular Disorders: vein discoloration, vein distention, hypertension,

Skin and Subcutaneous Tissue Disorders: allergic dermatitis, rash

ALOXI Capsules
The infrequently (<1%) reported adverse reactions listed below, assessed by investigators as treatment-related or causality unknown/missing, occurred following administration of a single dose of 0.5 mg ALOXI Capsules to adult patients receiving concomitant cancer chemotherapy. In general, adverse reactions were similar between oral and I.V. formulations.

Cardiac Disorders: transient arrhythmia, first degree atrioventricular block, second degree atrioventricular block

Ear and Labyrinth Disorders: motion sickness

Eye Disorders: eye swelling

Gastrointestinal Disorders: gastritis, nausea

General Disorders and Administration Site Conditions: fatigue, chills

Investigations: blood bilirubin increased

Musculoskeletal and Connective Tissue Disorders: joint stiffness, myalgia, pain in extremity

Nervous System Disorders: dysgeusia

Psychiatric Disorders: insomnia

Respiratory, Thoracic and Mediastinal Disorders: dyspnea
Skin and Subcutaneous Tissue Disorders: generalized pruritus, erythema

Post-Market Adverse Drug Reactions

The following adverse reactions have been identified during post-approval 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.

Hypersensitivity reactions and injection site reactions (burning, induration, discomfort and pain), convulsive events, and syncope.

DRUG INTERACTIONS

Overview
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.

Drug-Drug Interactions
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.

Palonosetron did not inhibit the antitumor activity of the five chemotherapeutic agents tested (cisplatin, cyclophosphamide, cytarabine, doxorubicin and mitomycin C) in murine tumor models.

Coadministration of a single dose 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 a single dose of palonosetron 0.25 mg (I.V. bolus) was administered on Day 1 and oral aprepitant for 3 days (125mg/80mg/80mg), the pharmacokinetics of palonosetron were not significantly altered (AUC: no change, C_{max}: 15% increase).

Concomitant administration of an antacid (Maalox® liquid 30 mL) had no effect on the oral absorption or pharmacokinetics of a single capsule of palonosetron 0.75 mg in healthy subjects.

Prolonged nausea, vomiting and abdominal cramps were reported in patients co-administered with ALOXI 0.25 mg I.V. and atropine prior to chemotherapy. The combination should be avoided.

In clinical trials, palonosetron has been safely administered with corticosteroids, analgesics, antiemetics/antinauseants and antispasmodic agents.

Serotonin Syndrome/Neuroleptic Malignant Syndrome-like events
As with other serotonergic agents, serotonin syndrome, a potentially life-threatening condition, may occur with 5-HT_3 receptor antagonist antiemetic treatment, particularly with concomitant use of other agents that may affect the serotonergic neurotransmitter system (including triptans, SSRIs, SNRIs, lithium, sibutramine, fentanyl and its analogues, dextromethorphan, tramadol, tapentadol, meperidine, methadone and pentazocine or St. John's Wort [Hypericum perforatum], and with drugs which impair metabolism of serotonin (such as MAOIs, including linezolid [an antibiotic which is a reversible non-selective MAOI], and methylene blue; See WARNINGS AND PRECAUTIONS.)

DOSAGE AND ADMINISTRATION

Dosing Considerations
ALOXI should be used only on the day of chemotherapy. Drug accumulation was observed in subjects administered ALOXI on consecutive days or once every two days for three doses. There is limited safety data available regarding repeated dosing of ALOXI (see Part II SCIENTIFIC INFORMATION/Detailed Pharmacology).

No dose adjustment is required for geriatric patients and patients with renal or hepatic impairment.

ALOXI has been shown to have similar safety profiles between initial and repeat courses of chemotherapy (see Part II SCIENTIFIC INFORMATION/Detailed Pharmacology).

Recommended Dose and Dosage Adjustment

ALOXI Injection
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.

The efficacy of ALOXI in the prevention of acute nausea and vomiting induced by highly emetogenic chemotherapy was demonstrated mainly in patients who were co-administered prophylactic corticosteroids (see CLINICAL TRIALS).

ALOXI Capsules
Dosage for Adults - one 0.5 mg capsule administered approximately one hour prior to the start of chemotherapy. ALOXI can be taken with or without food.

Administration

ALOXI Injection
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.

OVERDOSAGE

There is no known antidote to ALOXI. Overdose should be managed with supportive care.

Fifty adult cancer patients were administered palonosetron at an oral dose of 90 µg/kg (equivalent to 6 mg fixed dose in a 70 kg individual) as part of a dose ranging study. This is approximately 12 times the recommended oral dose of 0.5 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.

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action
Palonosetron is a 5-HT_3 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-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.

Pharmacodynamics
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 intravenously administered palonosetron at single

doses of 0.25 mg, 0.75 mg 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. However, a dose-dependent increase in maximum QTcI value on Day 1 (6.4, 7.5, 9.0 msec, although the maximum increase was below that of moxifloxacin at 12.9 msec) from baseline and the percentage of subjects with an increased QTcI at the 30 - 60 msec range (0%, 2.2%, 11%) were revealed in the three palonosetron dosing groups.

Pharmacokinetics

Absorption:

ALOXI Injection

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 ($AUC_{0-\infty}$) are generally dose proportional over the dose range of 0.3–90 µg/kg in healthy subjects and in cancer patients. Following administration of a single I.V. 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 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%.

ALOXI Capsules

Following oral administration, palonosetron is well absorbed with its absolute bioavailability reaching 97%. After single oral doses using buffered solution in healthy volunteers, mean maximum palonosetron concentrations (C_{max}) and area under the concentration-time curve ($AUC_{0-\infty}$) were dose proportional over the dose range of 3.0 to 80 µg/kg in healthy subjects. Mean time to maximum concentration ranged from 3.8 to 5.7 hours after oral dosing.

In 36 healthy male and female subjects given a single oral dose of ALOXI Capsules 0.5 mg, maximum plasma palonosetron concentration (C_{max}) was 0.81 ± 0.17 ng/mL (mean ± SD) and time to maximum concentration (T_{max}) was 5.1 ± 1.7 hours. In female subjects (n=18), the mean AUC was 35% higher and the mean C_{max} was 26% higher than in male subjects (n=18).

In 12 cancer patients given a single oral dose of palonosetron 0.5 mg one hour prior to chemotherapy, C_{max} was 0.93 ± 0.34 ng/mL and T_{max} was 5.1 ± 5.9 hours. The AUC was 30% higher in cancer patients than in healthy subjects. The mean PK parameters after a single oral dose of 0.5 mg palonosetron are compared between healthy subjects and cancer patients revealed in two studies (Table 3).

Table 3: Mean PK parameters[1] (± SD) of Palonosetron After a Single Dose of 0.5 mg ALOXI Capsules in Healthy Subjects and Cancer Patients

PK Parameters	Healthy subjects (n=36)	Cancer patients (n=12)
C_{max} (ng/mL)	0.81 ± 0.17	0.93 ± 0.34
T_{max} (h)	5.1 ± 1.7	5.1 ± 5.9
AUC_{∞} (ng•h/mL)	38.2 ± 11.7	49.7 ± 12.2
$t_{1/2}$ (h)	37 ± 12	48 ± 19

[1] a cross-study comparison

A high fat meal did not affect the C_{max} and AUC of oral palonosetron. Therefore, ALOXI Capsules may be taken without regard to meals.

Distribution:
Palonosetron has a volume of distribution of approximately 8.3 ± 2.5 L/kg. Approximately 62% of palonosetron (over palonosetron concentration range of 5.15 – 412 ng/mL) is bound to plasma proteins.

Metabolism:
Palonosetron is eliminated by multiple routes with approximately 50% metabolized to form two primary metabolites: N-oxide-palonosetron (account for 12.9% of the I.V. dose; 13.5% of the oral dose) and 6-S-hydroxy-palonosetron (account for 11.5% of the I.V. dose; 17.2% of the oral dose). 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. However, clinical pharmacokinetic parameters are not significantly different between poor and extensive metabolizers of CYP2D6 substrates.

Excretion:
ALOXI Injection
After a single intravenous dose of 10 µg/kg [^{14}C]-palonosetron to healthy subjects, approximately 80% of the dose was recovered within 144 hours in the urine. The amount of unchanged palonosetron excreted in urine represents approximately 42% 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 following a single I.V. dose of approximately 0.75 mg. Mean terminal elimination half-life was approximately 37 hours.

ALOXI Capsules
Following administration of a single oral 0.75 mg dose of [^{14}C]-palonosetron to six healthy subjects, 85% to 93% of the total radioactivity was excreted in urine, and 5% to 8% was eliminated in feces. In healthy subjects given ALOXI Capsules 0.5 mg, the terminal elimination half-life (t½) of palonosetron was approximately 37 hours (mean ± SD), and in cancer patients, t½ was ~48 hours (see Table 3).

Special Populations and Conditions

Geriatrics:
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.

In a cross-study comparison, after a single oral dose (0.75 mg) the systemic exposure of palonosetron (AUC) was similar, but mean C_{max} was 15% lower in healthy elderly subjects ≥ 65 years of age compared with the subjects < 65 years of age.

Gender:
ALOXI Capsules
Although a single dose of 0.5 mg ALOXI Capsule was associated with a 26-35% higher systemic exposure in female subjects than in male subjects, dosage adjustment is not necessary based on gender.

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 and systemic exposure ($AUC_{0-\infty}$) was 35% lower in Japanese male subjects compared to Caucasian males based on a cross-study comparison.

Similarly, oral pharmacokinetics of palonosetron were characterized in thirty-two healthy Japanese male subjects using solution over the dose range of 3-90 µg/kg. The apparent total body clearance was 26% higher in Japanese males than in Caucasian males based on a cross-study comparison.

No dose adjustment is necessary in Japanese subjects. The pharmacokinetics of palonosetron in other races have not been adequately characterized.

Hepatic Insufficiency:
Hepatic impairment does not significantly affect total body clearance of a single dose of intravenous palonosetron compared to the healthy subjects. The half-lives of palonosetron increased by 43% and 52% in patients with moderate and severe hepatic impairments (56 and 60 hours, respectively) compared to those of healthy subjects (39 hours). Systemic exposure decreased in patients with mild (by 27%) or severe (by 22%) hepatic impairment.

Renal Insufficiency:
Mild to moderate renal impairment does not significantly affect palonosetron pharmacokinetic parameters. The systemic exposure (AUC_{0-t}) to a single dose of intravenous ALOXI increased by approximately 45% in subjects with severe renal impairment relative to healthy subjects. Longer terminal half-lives (estimated 115-300 hours) were reported in 3 out of 7 patients with severe renal impairment compared to ~39 hours in healthy volunteers. The pharmacokinetics of palonosetron have not been studied in subjects with end-stage renal disease.

STORAGE AND STABILITY

ALOXI Injection
Store at 20-25ºC; excursions permitted from 15-30ºC. Protect from light.

ALOXI Capsules
Store at 20-25ºC; excursions permitted from 15-30ºC.

DOSAGE FORMS, COMPOSITION AND PACKAGING

ALOXI Injection
ALOXI (palonosetron hydrochloride), 0.25 mg (free base) in 5 mL, is supplied as a single-use sterile, clear, colourless solution in glass vials.

Inactive ingredients: mannitol, disodium edetate, and citrate buffer in water.

ALOXI Capsules
ALOXI (palonosetron hydrochloride) Capsules, 0.5 mg (free base), are supplied as light beige opaque soft gelatin capsules.

Inactive ingredients: monoglycerides and diglycerides of capryl/capric acid, gelatin, sorbitol, glycerin, water, polyglyceryl oleate, titanium dioxide, butylated hydroxyanisole, and black printing ink. May contain traces of medium chain triglyceride and lecithin.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

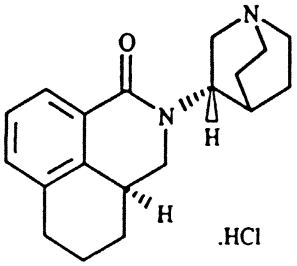
Proper name: palonosetron hydrochloride

Chemical name: (3aS)-2-[(S)-1-Azabicyclo [2.2.2]oct-3-yl]-2,3,3a,4,5,6-hexahydro-1-oxo-1*H*benz[*de*]isoquinoline hydrochloride

Molecular formula and molecular mass: $C_{19}H_{24}N_2O \cdot HCl$ 332.87

Structural formula:

Figure 1: Palonosetron Hydrochloride Structural Formula



Physicochemical properties: 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.

CLINICAL TRIALS

ALOXI Injection

Efficacy of single-dose (0.25 mg, 0.75 mg) palonosetron I.V. injection in preventing acute and delayed nausea and vomiting induced by moderately or highly emetogenic chemotherapy was studied in three Phase 3 trials. In these 3-arm double blind studies, efficacy was based on demonstrating non-inferiority of a single dose of ALOXI I.V. compared to ondansetron I.V. or dolasetron I.V. Non-inferiority criteria were met if the lower boundary of the two-sided 97.5% confidence interval for the difference in the complete response rate of palonosetron minus ondansetron or dolasetron was above -15% (non-inferiority margin 15%).

The primary endpoint was Complete Response (no emetic episode and no rescue medication) during the first 24 hours (acute phase) after chemotherapy. Secondary endpoints included Complete Response at further time periods (24-120 hours, delayed phase) and Complete Control (complete response and no more than mild nausea).

Moderately Emetogenic Chemotherapy

Two Phase 3, double-blind trials involving 1132 patients compared single-dose ALOXI I.V. with either single-dose I.V. ondansetron (Study 1) or I.V. 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, or methotrexate. 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%), Caucasian (65%, Hispanic: 31%) and naïve to previous chemotherapy (54%). The mean age was 55 years (18-97 years).

Table 4: Percentage of Patients[a] Responding by Treatment Group and Phase in the Moderately Emetogenic Chemotherapy Study versus Ondansetron

Time Period	I.V. ALOXI 0.25 mg (n= 189)	I.V. Ondansetron 32 mg (n= 185)	Difference I.V. ALOXI minus I.V. Ondansetron	Chi-square test
Complete Response			[Two sided 97.5% Confidence Interval][b]	p-value[c]
0 – 24 hours	81.0%	68.6%	12.4% [1.8%, 22.8%]	0.006
24 – 120 hours	74.1%	55.1%	19.0% [7.5%, 30.3%]	<0.001
0 – 120 hours	69.3%	50.3%	19.0% [7.4%, 30.7%]	<0.001
Complete Control			[Two sided 95% Confidence Interval]	p-value[d]
0 – 24 hours	76.2%	65.4%	10.8% [1.1%, 20.5%]	0.022
24 – 120 hours	66.7%	50.3%	16.4% [6.0%, 26.8%]	0.001
0 – 120 hours	63.0%	44.9%	18.1% [7.6%, 28.6%]	<0.001

[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 = 0.025
[d] Chi-square test. Significance level at α = 0.05
NS: not significant

Table 5: Percentage of Patients[a] Responding by Treatment Group and Phase in the Moderately Emetogenic Chemotherapy Study versus Dolasetron

Time Period	I.V. ALOXI 0.25 mg (n= 189)	I.V. Dolasetron 100 mg (n= 191)	Difference I.V. ALOXI minus I.V. Dolasetron	Chi-square test
Complete Response			[Two sided 97.5% Confidence Interval][b]	p-value[c]
0 – 24 hours	63.0%	52.9%	10.1% [-1.7%, 21.9%]	NS
24 – 120 hours	54.0%	38.7%	15.3% [3.4%, 27.1%]	0.003
0 – 120 hours	46.0%	34.0%	12.0% [0.3%, 23.7%]	0.017
Complete Control			[Two sided 95% Confidence Interval]	p-value[d]
0 – 24 hours	57.1%	47.6%	9.5% [-1%, 20%]	0.064
24 – 120 hours	48.1%	36.1%	12.0% [1.6%, 22.4%]	0.018
0 – 120 hours	41.8%	30.9%	10.9% [0.8%, 21%]	0.027

[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 = 0.025
[d] Chi-square test. Significance level at α = 0.05
NS: not significant

The two pivotal Phase 3 studies demonstrated non-inferiority of a single I.V. dose of palonosetron 0.25 mg in the prevention of acute nausea and vomiting associated with initial course of moderately emetogenic chemotherapy, vs. I.V. ondansetron 32 mg or I.V. dolasetron 100 mg. In addition, the difference in efficacy in Study 1 was statistically significant in favour of palonosetron (p=0.006) but was not statistically significant in Study 2.

Highly Emetogenic Chemotherapy

A Phase 3, double-blind trial involving 667 patients compared single dose ALOXI I.V. with single-dose I.V. ondansetron given 30 minutes prior to highly emetogenic chemotherapy including cisplatin ≥ 60 mg/m², cyclophosphamide, or dacarbazine. Dexamethasone, or in the event of a shortage, methylprednisolone, was co-administered prophylactically before chemotherapy in 67% of patients. Of the 667 patients, 51% were women, 60% Caucasian (Hispanic: 36%), and 59% naïve to previous chemotherapy. The mean age was 52 years (18-86 years).

Table 6: Percentage of Patients[a] Responding by Treatment Group and Phase in the Highly Emetogenic Chemotherapy Study versus Ondansetron

Time Period	I.V. ALOXI 0.25 mg (n= 223)	I.V. Ondansetron 32 mg (n= 221)	Difference I.V. ALOXI minus I.V. Ondansetron	Chi-square test
Complete Response			[Two sided 97.5% Confidence Interval][b]	p-value[c]
0 – 24 hours	59.2%	57.0%	2.2% [-8.8%, 13.1%]	NS
24 – 120 hours	45.3%	38.9%	6.4% [-4.6%, 17.3%]	NS
0 – 120 hours	40.8%	33.0%	7.8% [-2.9%, 18.5%]	NS
Complete Control			[Two sided 95% Confidence Interval]	p-value[d]
0 – 24 hours	56.5%	51.6%	4.9% [-4.8%, 14.6%]	0.298
24 – 120 hours	40.8%	35.3%	5.5% [-4%, 15%]	0.232
0 – 120 hours	37.7%	29.0%	8.7% [-0.5%, 17.9%]	0.052

[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 = 0.025
[d] Chi-square test. Significance level at α = 0.05
NS: not significant

A single I.V. dose of palonosetron 0.25 mg was shown to be non-inferior to I.V. ondansetron 32 mg in preventing acute nausea and vomiting following highly emetogenic chemotherapy.

Subgroup analysis suggested improved efficacy of ALOXI in combination with prophylactic corticosteroids compared to ALOXI alone (see Table 7).

Table 7: Patients with a Complete Response During the First 24 Hours after Highly Emetogenic Chemotherapy by Corticosteroid Use

0-24 h	Number (%) of patients with CR		Difference I.V. ALOXI minus I.V. Ondansetron [Two sided 97.5% Confidence Interval]	Pairwise testing* I.V. ALOXI vs. I.V. Ondansetron
	I.V. ALOXI 0.25 mg (n =223)	I.V. Ondansetron 32 mg (n = 221)		
With dexamethasone	97/150 (64.7%)	82/147 (55.8%)	8.9% [-4.5%; 22.2%]	0.118
Without dexamethasone	35/73 (47.9%)	44/74 (59.5%)	-11.5% [-31.2%; 8.2%]	0.162

* Chi-square p-values
NS: not significant

ALOXI Capsules

Moderately Emetogenic Chemotherapy
In a multicentre, randomized, double-blind active control clinical trial of 635 patients set to receive moderately emetogenic cancer chemotherapy including cyclophosphamide < 1500 mg/m^2, doxorubicin, carboplatin, epirubicin, or idarubicin. A single-dose of 0.25 mg, 0.5 mg, or 0.75 mg oral ALOXI capsules given one hour prior to moderately emetogenic chemotherapy was compared to a single-dose of 0.25 mg ALOXI I.V. given 30 minutes prior to chemotherapy. Patients were randomized to either dexamethasone or placebo in addition to their assigned treatment. The majority of patients in the study were women (73%), Caucasian (69%), and naïve to previous chemotherapy (59%).

The primary efficacy endpoint was Complete Response (no emetic episodes and no rescue medication) assessed in the acute phase (0-24 hours). Secondary efficacy endpoint included Complete Response assessed in the delayed phase (24-120 hours) and Complete Control.

Efficacy was based on demonstrating non-inferiority of oral palonosetron doses compared to the ALOXI I.V. formulation. Non-inferiority criteria were met if the lower bound of the two-sided 98.3% confidence interval for the difference in complete response rates of oral palonosetron dose minus the I.V. formulation was larger than -15%. The non-inferiority margin was 15%.

As shown in Table 8, ALOXI Capsules 0.5 mg demonstrated non-inferiority to the active comparator during the 0 to 24 hour time interval; however, for the 24 to 120 hour time period, non-inferiority was not shown.

Table 8: Proportion of Patients Achieving Complete Response and Complete Control Post-Chemotherapy – ALOXI Capsules

Time Period	Oral ALOXI 0.5 mg (N=160)	I.V. ALOXI 0.25 mg (N=162)	Difference Oral ALOXI minus I.V. ALOXI Comparator	Chi-square test
Complete Response			[Two-sided 98.3% Confidence Interval]*	p-value**
0-24 h	76.3%	70.4%	5.9% [-6.5%, 18.2%]	NS
24-120 h	62.5%	65.4%	-2.9% [-16.3%, 10.5%]	NS
0-120 h	58.8%	59.3%	-0.5% [-14.2%; 13.2%]	NS
Complete Control			[Two-sided 95% Confidence Interval]	p-value***
0-24 h	74.4%	68.5%	5.9% [-4.6% , 16.3%]	0.245
24-120 h	56.3%	62.3%	-4.0% [-17.4% , 5.2%]	0.266
0-120 h	52.5%	56.2%	-3.7% [-15.2% , 7.8%]	0.508

* To adjust for multiplicity of treatment groups, a lower-bound of a two-sided 98.3% confidence interval was used to compare -15%, the negative value of the non-inferiority margin.
** Chi-square test, significant level at α = 0.0167 adjusted for multiple comparisons
*** Chi-square test, significant level at α = 0.05
NS: not significant

Subgroup analysis suggested improved efficacy of ALOXI in combination with prophylactic corticosteroids compared to ALOXI alone (see Table 9).

Table 9: Patients with a Complete Response During the First 24 Hours after Moderately Emetogenic Chemotherapy by Corticosteroid Use

0-24 h	Number (%) of patients with CR		Difference ALOXI 0.5 mg minus I.V ALOXI 0.25 mg [Two-sided 98.3% Confidence Interval]	Pairwise testing* ALOXI 0.5 mg vs. I.V ALOXI 0.25 mg
	Oral ALOXI 0.5 mg (N=160)	I.V. ALOXI 0.25 mg (N=162)		
With dexamethasone	68/79 (86.1%)	68/82 (82.9%)	3.1% [-11.7; 18.0%]	0.581
Without dexamethasone	54/81 (66.7%)	46/80 (57.5%)	9.2 % [-10.2; 28.6%]	0.231

* Chi-square p-values
NS: not significant

DETAILED PHARMACOLOGY

Human

Pharmacokinetics in Repeat Dosing:

In a double-blind, randomized, placebo-controlled study, 12 healthy subjects received I.V. palonosetron 0.25 mg once daily for three consecutive days, and four subjects received placebo (a saline control). Palonosetron 0.25 mg I.V. daily for three consecutive days resulted in a 2.1-fold accumulation (ratio of Day 3 to Day 1 AUC_{0-24}).

Similarly, in a multi-centre, open-label study designed to assess the safety and efficacy of palonosetron 0.25 mg I.V. on Days 1, 3 and 5 to testicular cancer patients receiving 20 mg/m^2 cisplatin on Days 1 to 5 resulted in a 1.42-fold accumulation (ratio of Day 5 to Day 1 AUC_{0-t}]. On Day 5 after the third dose, the mean C_{max}, 2580 ng/L in the chemotherapy patients, was similar to the mean C_{max} of 2430 ng/L observed for healthy subjects on Day 3 after consecutive 0.25 mg daily I.V. doses.

Daily dosing of palonosetron in each study produced a similar PK profile and a predictable PK profile consistent with the long plasma elimination half-life of palonosetron of approximately 40 hours.

Use in multiple cycles:

Although comparative efficacy of IV and oral palonosetron in multiple cycles has not been demonstrated in controlled clinical studies, 875 patients enrolled in the three IV palonosetron phase 3 trials continued in an open label safety study and were treated with IV palonosetron 0.75mg for up to 9 additional cycles (median: 2 cycles) of chemotherapy. Moreover, 217 patients were enrolled in a multicenter, open label safety study and were treated with oral palonosetron 0.75 mg for up to 4 cycles (median: 3 cycles) of chemotherapy in a total of 654 chemotherapy cycles. The overall safety profiles were similar during all cycles in these studies.

Animal

Palonosetron is a potent and effective 5-HT_3 receptor antagonist and its antiemetic actions have been clearly demonstrated in a variety of *in vivo* studies. It has no clinically significant action on other serotonergic receptors.

In common with other 5-HT_3 receptor antagonists, palonosetron inhibits the I_{Kr} current and, at high concentrations, the I_{Na} current. These effects were demonstrated *in vitro*, but only at concentrations that far exceed those likely to be encountered in clinical use. They were not apparent in any *in vivo* study. There was evidence that palonosetron may have modest inhibitory activity at muscarinic receptor sites on sympathetic ganglia but there was no evidence of any other effect at pharmacologically relevant exposures. A number of other changes, such as convulsions in the single dose and repeat dose toxicity studies and arrhythmias in α_1-adrenoreceptor activated rabbits, suggest other possible actions but these were only apparent at fatal or near-fatal dosages. There was no evidence of any cardiovascular changes in the toxicity studies.

Preliminary dog Purkinje fibre *in vitro* data indicated that palonosetron increased the duration of action potential in this animal preparation

Although most *in vivo* studies were limited to intravenous dosages of up to 1 mg/kg, this is 300-fold higher than the proposed human dose. Day 1 toxicokinetics in dogs treated intravenously at this dosage suggest that the C_{max} was about 65-fold higher than the maximum expected human exposure. Exposures in the oral rat studies were probably sub-therapeutic.

In comparison to palonosetron, the two main metabolites found in humans (M9 and M4) demonstrated at least a 100-fold lower antagonistic activity at the 5-HT_3 receptor in an *in vitro* model of isolated guinea pig ileum. In addition, they were detected only in low or trace amounts in patients receiving palonosetron. The marginal 5-HT_3 antagonist activity of M4 and M9 is considered clinically non relevant.

There were significant differences in the rates and extent of metabolism in laboratory species when compared with those in humans. In man, there was relatively little metabolism of palonosetron, clearance was slow and there was an extended plasma half-life. Oral absorption was rapid in mice, rats and dogs. There was extensive metabolism in all animal species investigated and clearance was rapid. There was a significant first-pass effect in rats, dogs and primates following oral dosing, which was greatest in rats. Toxicokinetic studies suggest that this effect may be less marked in mice. The major human metabolites were present in rats and dogs; both trace human metabolites were also found in dogs, one of these was not found in rats. There was evidence that elimination mechanisms are saturated at high doses in animals, particularly rodents, and consequently exposure to palonosetron, and the human metabolites where present, was usually much greater than expected in human patients. Excretion was primarily urinary in all species including humans.

The pattern of major metabolites in rats, dogs and primates differed from each other and from humans. The plasma kinetics in monkeys are closer to those of dogs than humans. Palonosetron, but none of its metabolites, passes the blood-brain barrier in rats and was rapidly cleared from the brain, suggesting that it reaches the intended site of action and does not accumulate. There was evidence of reversible melanin binding of palonosetron or one of its metabolites in pigmented rats. No treatment-related ocular changes have been seen.

TOXICOLOGY

Single-Dose Toxicity

Deaths, in all species, were usually associated with convulsions and collapse. Other signs included inactivity, tremors, ataxia, laboured respiration, transient vocalisation in rats and emesis in dogs. There were no treatment-related signs in rats treated orally at 100 mg/kg or in dogs treated orally at up to 40 mg/kg. There were no effects associated with gender, or on body weight or food intake in any study, or on clinical pathology in dogs, and there were few necropsy observations.

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), equivalent to an oral dose of 500 mg/kg in rats and 100 mg/kg in dogs (7673 and 5115 times the recommended human oral dose, respectively, based on body surface area), was lethal. The maximum non-lethal dose was 20 mg/kg in both rats and dogs. The major signs of toxicity were convulsions, gasping, pallor, cyanosis and collapse.

Repeat-Dose Toxicity

Chronic intravenous administration to rats and oral treatment to mice at sub-lethal dosages was essentially without any evidence of toxicity. Treatment of dogs at marginally sublethal dosages, whether given orally or intravenously, was associated with convulsions, some other signs and, following oral treatment, a few minor clinical pathology changes, of which reduced alkaline phosphatase activity and increased cholesterol concentrations extended to lower oral dosages. There were no consistent pathology changes in dogs or mice, or in rats when treated intravenously. All of these studies were associated with high exposures to palonosetron.

In dogs deaths were clearly associated with severe signs including convulsions and the signs were generally associated with dosing and short-lived with rapid recovery. It seems likely that similar severe signs that were not observed directly were associated with the treatment-related deaths seen in mice and in intravenously treated rats.

Rats treated orally responded differently. There were numerous changes, including pathology, which extended to dosages well below those associated with increased mortality. Systemic exposure to palonosetron at the no observed adverse effect level was low compared with that following intravenous treatment to rats or dogs, although still well above that expected in human patients. Some of the deaths may have been associated with convulsions or other severe signs but it is probable that other toxic changes were more significant in rats treated orally.

Juvenile Toxicity Studies

Toxicity studies were conducted in neonatal rats and dogs. Rats were treated at Day 4 *post partum* by subcutaneous injection and dogs by intravenous injection from 2 weeks of age. In rats the main findings were dose-related changes at the injection sites, mainly in the high dose group (25 mg/kg/day). Other findings included reduction in body weight gains, mild anemia and increased number of lymphocytes but not histopathological changes. In neonatal dogs treated for 28 days with 6 mg/kg/day, there were no clinical or histopathological adverse effects.

Reproduction Toxicity

There was evidence that oral treatment with palonosetron at 60 mg/kg/day affected fertility in both male and female rats; this dosage is associated with histopathological changes in the seminiferous epithelium. A reduction in the number of viable foetuses in males treated intravenously at 10 mg/kg/day is not attributed to treatment.

Evidence of foetal toxicity was limited to low foetal weights in rats treated at 60 or 120 mg/kg/day during pregnancy, with an associated reduction in ossification. There was no similar effect in rabbits. In a pre- and post-natal study, there was evidence of maternal toxicity at 60 mg/kg/day. Postural changes in the F_1 generation were probably a consequence of this toxicity. There was no effect on development or reproduction in the F_1 generation. Juvenile toxicity studies did not show any evidence of toxicity that was not apparent in adult animals.

The no-observed-adverse-effect levels in each case were similar to or greater than those observed in repeat dose toxicity testing, suggesting that these changes only occur at exposures that significantly exceed those anticipated during clinical use.

Genotoxicity

The weight of evidence indicates that palonosetron lacks genotoxic activity. In the Salmonella

(Ames) reverse mutation test, there was no evidence for mutagenic activity. There was also no evidence for mutagenic activity of palonosetron in the CHO/HGPRT forward mutation assay. An *in vitro* chromosome aberration assay was conducted in CHO cells in which a clastogenic effect was observed in the absence of metabolic activation and an equivocal response with metabolic activation. An additional *in vitro* photo-chromosome aberration assay performed in V79 cells, was negative. In an *in vivo* micronucleus test in mice treated intravenously at up to 10 mg/kg, there was no evidence for mutagenic or clastogenic effects. Palonosetron was also tested in the *in vivo* Unscheduled DNA Synthesis test in rat hepatocytes at intravenous doses of up to 30mg/kg and there was no evidence for DNA damage. Overall, palonosetron is considered non-mutagenic.

Carcinogenicity

Two carcinogenicity studies in the mouse and rat were performed. Systemic exposure to palonosetron in these studies was not linear and increased with duration (Table 10).

Table 10: Systemic Exposure to Palonosetron During Carcinogenicity Testing

Species	Dosage mg/kg/day	Time	AUC, ng·h/mL		C_{max}, ng/mL	
			Male	Female	Male	Female
Mouse	60 [a]	Day 1	5475	4623	1534	1729
		Weeks 26-104	9757	5644	1788	1619
Rat	15	Day 1	39	39	19	26
		Weeks 26-104	296	443	148	261
	30 / 45	Day 1	362	480	153	141
		Weeks 26-104	1299	3405	410	947
	60 / 90	Day 1	1402	2511	427	703
		Weeks 26-104	5370	10024	1420	1824

[a] Highest dosage = NOAEL.

In the mouse study the only statistically significant tumour incidence was in males treated at 10 mg/kg/day in respect of the combined incidence of malignant lymphoma and malignant pleomorphic lymphoma. The incidences of these common tumour types were clearly unaffected at higher dosages and the finding was not attributed to treatment. Exposure to palonosetron at the high dosage in terms of the AUCs was more than 1100-fold higher in males, and 650-fold higher in females, than found in human patients at the proposed clinical dose.

In the rat study, toxicity was apparent at all dosages although at 15 mg/kg/day this was confined to increased incidences of ungroomed coat and salivation with associated brown staining, increased liver weights and, in males only, increased accumulations of alveolar macrophages in

the lungs. In addition to these, toxic changes at the highest dosage included increased mortality, reduced body weights and erythrocyte counts, increased hemosiderosis in the spleen, medullary hyperplasia in the adrenals, progressive nephropathy, clear cell foci in the liver, secretory activity and acinar hyperplasia in the mammary gland, degeneration of the tubular germinal epithelium in the testis, epithelial hyperplasia and/or cysts in the thymus, C-cell hyperplasia in the thyroid, keratin cysts in the skin and hyperplastic and inflammatory lesions in the tail.

In the rat study, there were statistically significant increased incidences of a variety of tumours affecting the adrenal, liver, mammary gland, pancreas, pituitary, skin, tail and thyroid. These tumours occurred at high doses (30 and 60 mg/kg/day) administered for 2 years. Although the underlying mechanism of palonosetron tumorigenicity is not known, it may be associated with disruption of neuroendocrine pathways.

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PART III: CONSUMER INFORMATION

ALOXI®
(palonosetron injection)
as palonosetron hydrochloride

This leaflet is part III of a three-part "Product Monograph" published when ALOXI was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about ALOXI. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
ALOXI (Ah-lock-see) is used in adult patients to prevent nausea and vomiting that may happen after taking certain anti-cancer medicines (chemotherapy).

What it does:
ALOXI is a medicine called an "antiemetic". ALOXI blocks the action of the natural substance, serotonin, which can cause nausea and vomiting.

When it should not be used:
Do not take ALOXI if you are allergic to palonosetron hydrochloride or any of the other ingredients in ALOXI injection.

What the medicinal ingredient is:
Palonosetron hydrochloride

What the non-medicinal ingredients are:
Citrate buffer in water, disodium edetate, mannitol

What dosage forms it comes in:
ALOXI is supplied as a single-use sterile, clear, colorless solution in glass vials. Each 5 ml vial contains 0.25 mg palonosetron as palonosetron hydrochloride.

WARNINGS AND PRECAUTIONS

BEFORE you use ALOXI talk to your doctor or pharmacist if:

- you have any heart disorder, including an irregular heartbeat, prolongation of the QT interval or a family history of QT prolongation or sudden cardiac death at less than 50 years
- you have low levels of potassium or magnesium
- you have high blood pressure
- you have liver or kidney problems
- you have acute bowel obstruction or a history of repeated constipation
- you are pregnant or are planning to become pregnant
- you are breast-feeding or plan to breast-feed
- you are allergic to other 5-HT_3 receptor antagonists such as ondansetron, dolasetron, or granisetron

Serotonin Syndrome is a rare but potentially life-threatening reaction that can occur with "antiemetic" medicines. It can cause serious changes in how your brain, muscles and digestive system work.
Serotonin Syndrome symptoms include:

- fever, sweating, shivering, diarrhea, nausea, vomiting;
- muscle shakes, jerks, twitches or stiffness, overactive reflexes, loss of coordination;
- fast heartbeat, changes in blood pressure;
- confusion, agitation, restlessness, hallucinations, mood changes, unconsciousness, and coma.

The reaction is more likely to occur if you also take certain other medications. Be sure to tell your healthcare professional all the medicines you are taking.

ALOXI may cause severe allergic reaction. Symptoms include swelling of the face, lips or tongue, difficulty breathing, rash, or fainting.

Do not take ALOXI if you are less than 18 years old.

INTERACTIONS WITH THIS MEDICATION

As with most medicines, interactions with other drugs are possible. To avoid potentially life-threatening reactions, tell your healthcare professional about **ALL** the medicines you take, including drugs prescribed by other doctors, vitamins, minerals, natural supplements, or alternative medicines.

PROPER USE OF THIS MEDICATION

Usual dose:
0.25 mg is given to you as an injection into the vein (intravenous) over 30 seconds, and about 30 minutes before you get your anti-cancer medicine (chemotherapy).

Overdose:

If you take more ALOXI than you should or in case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The possible side effects are:
Common: headache, constipation, diarrhea, dizziness
Uncommon: tiredness (fatigue), abdominal pain , trouble sleeping (insomnia)

Tell your health professional about any side effect that bothers you or that does not go away.

Serious allergic reactions can happen with ALOXI. Tell your doctor if you experience redness or swelling of the skin, itching, chest discomfort or shortness of breath.

These are not all the possible side effects with ALOXI. For more information, ask your health professional.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		**Talk with your doctor or pharmacist**		**Stop taking drug and call your doctor or pharmacist**
		Only if severe	**In all cases**	
Common (≥1%)	**Headache**	√		
	Constipation	√		
	Diarrhea	√		
	Dizziness	√		
Uncommon (<1%)	**Fatigue**	√		
	Abdominal pain		√	
	Insomnia (trouble sleeping)	√		
Very Rare	**Allergic reaction (swelling of the lips, face, tongue or throat, difficulty in breathing, rash, hives)**			√

This is not a complete list of side effects. For any unexpected effects while taking ALOXI, contact your doctor or pharmacist.

HOW TO STORE IT

Store at 20-25ºC; excursions permitted from 15-30ºC. Protect from light.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

Report online at www.healthcanada.gc.ca/medeffect
Call toll-free at 1-866-234-2345
Complete a Canada Vigilance Reporting Form and:
- Fax toll-free to 1-866-678-6789, or
- Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701D
Ottawa, Ontario
K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, Purdue Pharma, at: 1-800-387-5349

This leaflet was prepared by Purdue Pharma, Pickering, ON L1W 3W8.

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Last revised: April 10, 2017.

PART III: CONSUMER INFORMATION

ALOXI®
(palonosetron capsules)
as palonosetron hydrochloride

This leaflet is part III of a three-part "Product Monograph" published when ALOXI was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about ALOXI. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
ALOXI (Ah-lock-see) is a prescription medicine used in adults to help prevent the acute nausea and vomiting that happens with certain anti-cancer medicines (chemotherapy).

What it does:
ALOXI is a medicine called an "antiemetic". ALOXI blocks the action of the natural substance, serotonin, which can cause nausea and vomiting.

When it should not be used:
Do not take ALOXI if you are allergic to palonosetron hydrochloride or any of the other ingredients in ALOXI capsules.

What the medicinal ingredient is:
Palonosetron hydrochloride

What the non-medicinal ingredients are:
Monoglycerides and diglycerides of capryl/capric acid, gelatin, sorbitol, glycerin, water, polyglyceryl oleate, titanium dioxide, butylated hydroxyanisole, and black printing ink. May contain traces of medium chain triglyceride and lecithin.

What dosage forms it comes in:
ALOXI is available in light beige opaque soft gelatine capsules. Each capsule contains 0.5 mg palonosetron as palonosetron hydrochloride.

WARNINGS AND PRECAUTIONS

BEFORE you use ALOXI talk to your doctor or pharmacist if:

- you have any heart disorder, including an irregular heartbeat, prolongation of the QT interval or a family history of QT prolongation or sudden cardiac death at less than 50 years
- you have low levels of potassium or magnesium
- you have high blood pressure
- you have liver or kidney problems
- you have acute bowel obstruction or a history of repeated constipation
- you are pregnant or are planning to become pregnant
- you are breast-feeding or plan to breast-feed
- you are allergic to other 5-HT_3 receptor antagonists such as ondansetron, dolasetron, or granisetron

Serotonin Syndrome is a rare but potentially life-threatening reaction that can occur with "antiemetic" medicines. It can cause serious changes in how your brain, muscles and digestive system work.
Serotonin Syndrome symptoms include:

- fever, sweating, shivering, diarrhea, nausea, vomiting;
- muscle shakes, jerks, twitches or stiffness, overactive reflexes, loss of coordination;
- fast heartbeat, changes in blood pressure;
- confusion, agitation, restlessness, hallucinations, mood changes, unconsciousness, and coma.

The reaction is more likely to occur if you also take certain other medications. Be sure to tell your healthcare professional all the medicines you are taking.

ALOXI may cause severe allergic reaction. Symptoms include swelling of the face, lips or tongue, difficulty breathing, rash, or fainting.

Do not take ALOXI if you are less than 18 years old.

INTERACTIONS WITH THIS MEDICATION

As with most medicines, interactions with other drugs are possible. To avoid potentially life-threatening reactions, tell your healthcare professional about **ALL** the medicines you take, including drugs prescribed by other doctors, vitamins, minerals, natural supplements, or alternative medicines.

PROPER USE OF THIS MEDICATION

Usual dose:
0.5 mg (one capsule) by mouth about an hour before you get your anti-cancer medicine (chemotherapy). ALOXI can be taken with or without food.

Overdose:

If you take more ALOXI than you should or in case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The possible side effects are:
Common: headache, constipation
Uncommon: tiredness (fatigue)

Tell your doctor if you have any side effect that bothers you or that does not go away.

Serious allergic reactions can happen with ALOXI. Tell your doctor if you experience redness or swelling of the skin, itching, chest discomfort or shortness of breath.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common (>1%)	**Headache**	√		
Uncommon (≤1%)	**Fatigue**	√		
	Constipation	√		
Very Rare	**Allergic reaction (swelling of the lips, face, tongue or throat, difficulty in breathing, rash, hives)**			√

This is not a complete list of side effects. For any unexpected effects while taking ALOXI, contact your doctor or pharmacist.

HOW TO STORE IT

Store at 20-25ºC; excursions permitted from 15-30ºC.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

Report online at www.healthcanada.gc.ca/medeffect
Call toll-free at 1-866-234-2345
Complete a Canada Vigilance Reporting Form and:
- Fax toll-free to 1-866-678-6789, or
- Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701D
Ottawa, Ontario
K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, Purdue Pharma, at: 1-800-387-5349

This leaflet was prepared by Purdue Pharma, Pickering, ON L1W 3W8.

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