

References: 1. Gralla R, Liebman M, Van der Vliet A, et al. Palonosetron improves prevention of chemotherapy-induced nausea and vomiting following moderately emetogenic chemotherapy: results of a double-blind randomized phase III trial comparing single doses of palonosetron with ondansetron. *Ann Oncol.* 2003;14:1570-1577. 2. Eisenberg P, Figueroa-Velazquez J, Zanon R, et al. Improved prevention of moderately emetogenic chemotherapy-induced nausea and vomiting with palonosetron, a pharmacologically novel 5-HT₃ receptor antagonist results of a phase III, single-dose trial versus dolasetron. *Cancer.* 2003;98:2473-2482. 3. Hübner B, Gralla RJ, Eisenberg P, et al. Palonosetron (PALO) compared with ondansetron (ONDO) or dolasetron (DOLA) for prevention of acute & delayed chemotherapy-induced nausea and vomiting (CINV): combined results of two phase III trials. *Proc Am Soc Clin Oncol.* 2003;22:229. Abstract 2032. 4. NCCN Practice Guidelines in Oncology—v.1.2005 Antineoplastic, Supportive Care Network. Available at: http://www.nccn.org/professionals/physician_gf/PDF/antineoplas.pdf. Accessed February 24, 2005. 5. ALOXI® (palonosetron HCl) injection full prescribing information. 6. Anzemet® (dolasetron mesylate) full prescribing information. 7. Zofran® (ondansetron hydrochloride) full prescribing information. 8. Zofran® (ondansetron hydrochloride) full prescribing information. 9. Weng EHE, Clark R, Leung E, et al. The interaction of RS 25201-157, a potent and selective antagonist, with 5-HT₃ receptors *in vivo*. *Br J Pharmacol.* 1995;114:871-881. 10. Miller FC, Galvan M, Gross MR, van Gorkom EDM, Mose PC, Fozard JR. Pharmacological properties of dolasetron, a potent and selective antagonist at 5-HT₃ receptors. *Drug Dev Res.* 1992;26:67-70.

Aloxi[®]

palonosetron HCl injection

BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE

ALOXI is indicated for:

- 1) the prevention of acute nausea and vomiting associated with initial and repeat courses of moderately and highly emetogenic cancer chemotherapy, and
- 2) the prevention of delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy.

CONTRAINDICATIONS

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

PRECAUTIONS

General

Hypersensitivity reactions may occur in patients who have exhibited hypersensitivity to other selective 5-HT₃ receptor antagonists. Although palonosetron has been safely administered to 192 patients with pre-existing cardiac impairment in the Phase 3 studies, ALOXI should be administered with caution in patients who have or may develop prolongation of cardiac conduction intervals, particularly QTc. These include patients with hypokalemia or hyponagnesemia, patients taking diuretics with potential for inducing electrolyte abnormalities, patients with congenital QT syndrome, patients taking anti-arrhythmic drugs or other drugs which lead to QT prolongation, and cumulative high dose anti-neoplastic therapy. In 3 pivotal trials, ECGs were obtained at baseline and 24 hours after subjects received palonosetron or a comparator drug. In a subset of patients ECGs were also obtained 15 minutes following dosing. The percentage of patients (<1%) with changes in QT and QTc intervals (either absolute values of > 50 msec or changes of > 60 msec from baseline) was similar to that seen with the comparator drugs.

Drug Interactions

Palonosetron is eliminated from the body through both renal excretion and metabolic pathways. Therefore, the potential for clinically significant drug interactions with palonosetron appears to be low (See CLINICAL PHARMACOLOGY, Drug-Drug Interactions section of the Full Prescribing Information).

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 104-week carcinogenicity study in CD-1 mice, animals were treated with oral doses of palonosetron at 10, 30 and 60 mg/kg/day. Treatment with palonosetron was not tumorigenic. The highest tested dose produced a systemic exposure to palonosetron (Plasma AUC of about 150 to 289 times the human exposure [AUC₀₋₂₄ = 29.8 ng•h/ml] at the recommended intravenous dose of 0.25 mg. In a 104-week carcinogenicity study in Sprague-Dawley rats, male and female rats were treated with oral doses of 15, 30 and 60 mg/kg/day and 15, 45 and 90 mg/kg/day, respectively. The highest doses produced a systemic exposure to palonosetron (Plasma AUC of 137 and 308 times the human exposure at the recommended dose. Treatment with palonosetron produced increased incidences of adrenal benign pheochromocytoma and combined benign and malignant pheochromocytoma, increased incidences of pancreatic islet cell adenoma and combined adenoma and carcinoma and pituitary adenoma in male rats. In female rats, it produced hepatocellular adenoma and carcinoma and increased the incidences of thyroid C-cell adenoma and combined adenoma and carcinoma.

Palonosetron was not genotoxic in the Ames test, the Chinese hamster ovarian cell (CHO)HPRT forward mutation test, the *in vivo* hepatocyte unscheduled DNA synthesis (UDS) test or the mouse micronucleus test. It was, however, positive for clastogenic effects in the Chinese hamster ovarian (CHO) cell chromosomal aberration test.

Palonosetron at oral doses up to 60 mg/kg/day (about 1894 times the recommended human intravenous dose based on body surface area) was found to have no effect on fertility and reproductive performance of male and female rats.

Pregnancy, Teratogenic Effects: Category B

Teratology studies have been performed in rats at oral doses up to 60 mg/kg/day (1894 times the recommended human intravenous dose based on body surface area) and rabbits at oral doses up to 60 mg/kg/day (3789 times the recommended human intravenous dose based on body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to palonosetron. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, palonosetron should be used during pregnancy only if clearly needed.

Labor and Delivery

Palonosetron has not been administered to patients undergoing labor and delivery, so its effects on the mother or child are unknown.

Nursing Mothers

It is not known whether palonosetron is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants and the potential for tumorigenicity shown for palonosetron in the rat carcinogenicity study, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

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

Geriatric Use

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 adjustments or special monitoring are required for geriatric patients.

ADVERSE REACTIONS

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

Event	ALOXI 0.25 mg (N=633)	Ondansetron 32 mg IV (N=410)	Dolasetron 100 mg IV (N=194)
Headache	60 (9%)	34 (8%)	32 (16%)
Constipation	29 (5%)	8 (2%)	12 (6%)
Diarrhea	8 (1%)	7 (2%)	4 (2%)
Dizziness	8 (1%)	9 (2%)	4 (2%)
Fatigue	3 (<1%)	4 (1%)	4 (2%)
Abdominal Pain	1 (<1%)	2 (<1%)	3 (2%)
Insomnia	1 (<1%)	3 (1%)	3 (2%)

In other studies, 2 subjects experienced severe constipation following a single palonosetron dose of approximately 0.75 mg, three times the recommended dose. One patient received a 10 µg/kg oral dose in a post-operative nausea and vomiting study and one healthy subject received a 0.75 mg IV 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.

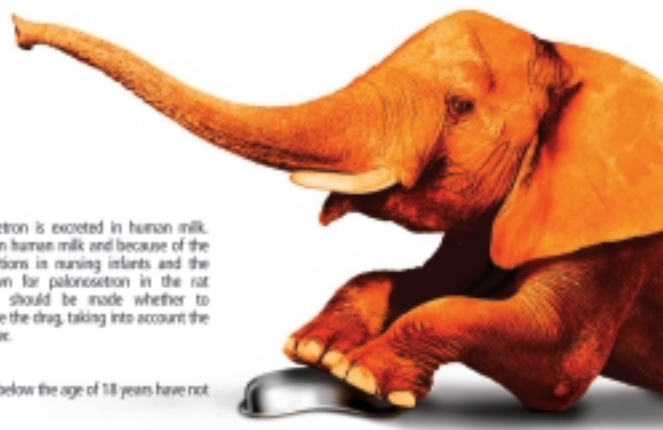
Hearing and Vision: < 1%: motion sickness, tinnitus, eye irritation and amblyopia.

Gastrointestinal System: 1%: diarrhea, < 1%: dyspepsia, abdominal pain, dry mouth, hiccup 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, hypoglycemia, 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.

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 µg/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.

DOSE AND ADMINISTRATION

Dosage for Adults

The recommended dosage of ALOXI is 0.25 mg administered as a single dose approximately 30 minutes before the start of chemotherapy. Repeated dosing of ALOXI[®] within a seven day interval is not recommended because the safety and efficacy of frequent (consecutive or alternate day) dosing in patients has not been evaluated.

Use in Geriatric Patients and in Patients with Impaired Renal or Hepatic Function

No dosage adjustment is recommended.

Dosage for Pediatric Patients

A recommended intravenous dosage has not been established for pediatric patients.

Administration

ALOXI is to be infused intravenously over 30 seconds. ALOXI should not be mixed with other drugs. Flush the infusion line with normal saline before and after administration of ALOXI.

NDC Number 58063-797-25

Prescribing information as of July 2004

MfD by Cardinal Health, Albuquerque, NM, USA and Helsinn Biotech Pharmaceuticals, Dublin, Ireland

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