

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ALOXI safely and effectively. See full prescribing information for ALOXI.

**ALOXI® (palonosetron HCl) Injection for Intravenous Use**  
Initial U.S. Approval: 2003

### RECENT MAJOR CHANGES

Dosage and Administration, Recommended Dosing (2.1) 08/2007

### INDICATIONS AND USAGE

ALOXI is a serotonin subtype 3 (5-HT<sub>3</sub>) receptor antagonist indicated for:

- Moderately emetogenic cancer chemotherapy -- prevention of acute and delayed nausea and vomiting associated with initial and repeat courses (1.1)
- Highly emetogenic cancer chemotherapy -- prevention of acute nausea and vomiting associated with initial and repeat courses (1.1)

### DOSAGE AND ADMINISTRATION

Adult Dosage: a single 0.25 mg I.V. dose administered over 30 seconds. Dosing should occur approximately 30 minutes before the start of chemotherapy (2.1).

### DOSAGE FORMS AND STRENGTHS

0.25 mg/5 mL (free base) single-use vial (3)

### CONTRAINDICATIONS

ALOXI is contraindicated in patients known to have hypersensitivity to the drug or any of its components (4)

### WARNINGS AND PRECAUTIONS

- Hypersensitivity reactions may occur in patients who have exhibited hypersensitivity to other 5-HT<sub>3</sub> receptor antagonists (5.1)
- Administer with caution in patients who have or may develop prolongation of cardiac conduction intervals, particularly QTc (5.2)

### ADVERSE REACTIONS

The most common adverse reactions (incidence ≥5%) are headache and constipation (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact MGI PHARMA at 1-800-562-5580 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).**

### DRUG INTERACTIONS

The potential for clinically significant drug interactions with palonosetron appears to be low (7)

### USE IN SPECIFIC POPULATIONS

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

**See 17 for PATIENT COUNSELING INFORMATION and FDA-Approved Patient Labeling**

Revised: 08/2007

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\* Sections or subsections omitted from the full prescribing information are not listed.

# Aloxi® (palonosetron HCl) injection

## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

#### 1.1 Prevention of 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 nausea and vomiting associated with initial and repeat courses

### 2 DOSAGE AND ADMINISTRATION

#### 2.1 Recommended Dosing

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

#### 2.2 Instructions for 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.

### 3 DOSAGE FORM AND STRENGTHS

ALOXI is supplied as a single-use sterile, clear, colorless solution in glass vials that provides 0.25 mg (free base) per 5 mL.

### 4 CONTRAINDICATIONS

ALOXI is contraindicated in patients known to have hypersensitivity to the drug or any of its components. [see *Adverse Reactions* (6.2)]

### 5 WARNINGS AND PRECAUTIONS

#### 5.1 Hypersensitivity

Hypersensitivity reactions may occur in patients who have exhibited hypersensitivity to other 5-HT<sub>3</sub> receptor antagonists.

#### 5.2 QTc Intervals

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 hypomagnesemia, 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 anthracycline 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 > 500 msec or changes of > 60 msec from baseline) was similar to that seen with the comparator drugs.

### 6 ADVERSE REACTIONS

#### 6.1 Clinical Trials Experience

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 reported in practice.

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 mcg/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, 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.

#### 6.2 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 and injection site reactions (burning, induration, discomfort and pain) were reported from postmarketing experience.

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### 7 DRUG INTERACTIONS

Palonosetron is eliminated from the body through both renal excretion and metabolic pathways with the latter mediated via multiple CYP enzymes. *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.

A study in healthy volunteers involving single-dose IV 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.

### 8 USE IN SPECIFIC POPULATIONS

#### 8.1 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.

#### 8.2 Labor and Delivery

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

#### 8.3 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.

#### 8.4 Pediatric Use

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

#### 8.5 Geriatric Use

Population pharmacokinetics analysis did not reveal any differences in palonosetron pharmacokinetics between cancer patients  $\geq 65$  years of age and younger patients (18 to 64 years). Of the 1374 adult cancer patients in clinical studies of palonosetron, 316 (23%) were  $\geq 65$  years old, while 71 (5%) were  $\geq 75$  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.

#### 8.6 Renal Impairment

Mild to moderate renal impairment does not significantly affect palonosetron pharmacokinetic parameters. Total systemic exposure increased by approximately 28% in severe renal impairment relative to healthy subjects. Dosage adjustment is not necessary in patients with any degree of renal impairment.

#### 8.7 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.

#### 8.8 Race

Intravenous palonosetron pharmacokinetics was characterized in twenty-four healthy Japanese subjects over the dose range of 3 – 90 mcg/kg.

Total body clearance was 25% higher in Japanese subjects compared to Whites, however, no dose adjustment is required. The pharmacokinetics of palonosetron in Blacks has not been adequately characterized.

### 10 OVERDOSAGE

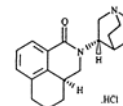
There is no known antidote to ALOXI. Overdose should be managed with supportive care.

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.

### 11 DESCRIPTION

ALOXI is an antiemetic and antinauseant agent. It is a serotonin subtype 3 (5-HT<sub>3</sub>) receptor antagonist with a strong binding affinity for this receptor. Chemically, palonosetron hydrochloride is: (3aS)-2-[(S)-1-Azabicyclo [2.2.2]oct-3-yl]-2,3,3a,4,5,6-hexahydro-1-oxo-1Hbenz[de]isoquinoline hydrochloride. The empirical formula is C<sub>19</sub>H<sub>24</sub>N<sub>2</sub>O.HCl, with a molecular weight of 332.87. Palonosetron hydrochloride exists as a single isomer and has the following structural formula:



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.

ALOXI Injection is a sterile, clear, colorless, non-pyrogenic, isotonic, buffered solution for intravenous administration. Each 5 mL vial of ALOXI Injection contains 0.25 mg palonosetron base as hydrochloride, 207.5 mg mannitol, disodium edetate and citrate buffer in water for intravenous administration. The pH of the solution is 4.5 to 5.5.

### 12 CLINICAL PHARMACOLOGY

#### 12.1 Mechanism of Action

Palonosetron is a 5-HT<sub>3</sub> 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<sub>3</sub> 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<sub>3</sub> receptors located on vagal afferents to initiate the vomiting reflex.

#### 12.2 Pharmacodynamics

The effect of palonosetron on blood pressure, heart rate, and ECG parameters including QTc were comparable to ondansetron and dolasetron in clinical trials. 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. In clinical trials, the dose-response relationship to the QTc interval has not been fully evaluated.

#### 12.3 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 (C<sub>max</sub>) and area under the concentration-time curve (AUC<sub>0-∞</sub>) are generally dose-proportional over the dose range of 0.3–90 mcg/kg in healthy subjects and in

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cancer patients. Following single IV dose of palonosetron at 3 mcg/kg (or 0.21 mg/70 kg) to six cancer patients, mean ( $\pm$ SD) maximum plasma concentration was estimated to be  $5.6 \pm 5.5$  ng/mL and mean AUC was  $35.8 \pm 20.9$  ng•hr/mL. Following IV 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  $42 \pm 34\%$ . Following IV administration of palonosetron 0.25 mg once daily for 3 days in 12 healthy subjects, the mean ( $\pm$ SD) increase in plasma palonosetron concentration from Day 1 to Day 3 was  $110 \pm 45\%$ .

### 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<sub>3</sub> 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.

### Elimination

After a single intravenous dose of 10 mcg/kg [<sup>14</sup>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 was approximately 40 hours.

### Special Populations

[See USE IN SPECIFIC POPULATIONS (8.5 – 8.8)]

## 13 NONCLINICAL TOXICOLOGY

### 13.1 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 (AUC = 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/HGPR1) forward mutation test, the *ex 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.

## 14 CLINICAL STUDIES

Efficacy of single-dose palonosetron injection in preventing acute and delayed nausea and vomiting induced by both moderately and highly emetogenic chemotherapy was studied in three Phase 3 trials and one Phase 2 trial. In these double-blind studies, complete response rates (no emetic

episodes and no rescue medication) and other efficacy parameters were assessed through at least 120 hours after administration of chemotherapy. The safety and efficacy of palonosetron in repeated courses of chemotherapy was also assessed.

### Moderately Emetogenic Chemotherapy

Two Phase 3, double-blind trials involving 1132 patients compared single-dose IV ALOXI with either single-dose IV ondansetron (study 1) or dolasetron (study 2) given 30 minutes prior to moderately emetogenic chemotherapy including carboplatin, cisplatin  $\leq 50$  mg/m<sup>2</sup>, cyclophosphamide  $< 1500$  mg/m<sup>2</sup>, doxorubicin  $> 25$  mg/m<sup>2</sup>, epirubicin, irinotecan, and methotrexate  $> 250$  mg/m<sup>2</sup>. Concomitant corticosteroids were not administered prophylactically in study 1 and were used by 4-6% of patients in study 2. The majority of patients in these studies were women (77%), White (65%) and naive to previous chemotherapy (54%). The mean age was 55 years.

### Highly Emetogenic Chemotherapy

A Phase 2, double-blind, dose-ranging study evaluated the efficacy of single-dose IV palonosetron from 0.3 to 90 mcg/kg (equivalent to  $< 0.1$  mg to 6 mg fixed dose) in 161 chemotherapy-naïve adult cancer patients receiving highly-emetogenic chemotherapy (either cisplatin  $\geq 70$  mg/m<sup>2</sup> or cyclophosphamide  $> 1100$  mg/m<sup>2</sup>). Concomitant corticosteroids were not administered prophylactically. Analysis of data from this trial indicates that 0.25 mg is the lowest effective dose in preventing acute nausea and vomiting induced by highly emetogenic chemotherapy.

A Phase 3, double-blind trial involving 667 patients compared single-dose IV ALOXI with single-dose IV ondansetron (study 3) given 30 minutes prior to highly emetogenic chemotherapy including cisplatin  $\geq 60$  mg/m<sup>2</sup>, cyclophosphamide  $> 1500$  mg/m<sup>2</sup>, and dacarbazine. Corticosteroids were co-administered prophylactically before chemotherapy in 67% of patients. Of the 667 patients, 51% were women, 60% White, and 59% naïve to previous chemotherapy. The mean age was 52 years.

### Efficacy Results

The antiemetic activity of ALOXI was evaluated during the acute phase (0-24 hours) [Table 2], delayed phase (24-120 hours) [Table 3], and overall phase (0-120 hours) [Table 4] post-chemotherapy in Phase 3 trials.

Table 2: Prevention of Acute Nausea and Vomiting (0-24 hours): Complete Response Rates

| Chemotherapy          | Study | Treatment Group      | N <sup>a</sup> | % with Complete Response | p-value <sup>b</sup> | <b>97.5% Confidence Interval<br/>ALOXI minus Comparator<sup>c</sup></b><br> |
|-----------------------|-------|----------------------|----------------|--------------------------|----------------------|---|
| Moderately Emetogenic | 1     | ALOXI 0.25 mg        | 189            | 81                       | 0.009                |   |
|                       |       | Ondansetron 32 mg IV | 185            | 69                       |                      |   |
|                       | 2     | ALOXI 0.25 mg        | 189            | 63                       | NS                   |   |
|                       |       | Dolasetron 100 mg IV | 191            | 53                       |                      |   |
| Highly Emetogenic     | 3     | ALOXI 0.25 mg        | 223            | 59                       | NS                   |   |
|                       |       | Ondansetron 32 mg IV | 221            | 57                       |                      |   |

a Intent-to-treat cohort

b 2-sided Fisher's exact test. Significance level at  $\alpha=0.025$ .

c These studies were designed to show non-inferiority. A lower bound greater than  $-15\%$  demonstrates non-inferiority between ALOXI and comparator.

These studies show that ALOXI was effective in the prevention of acute nausea and vomiting associated with initial and repeat courses of moderately and highly emetogenic cancer chemotherapy. In study 3, efficacy was greater when prophylactic corticosteroids were administered concomitantly. Clinical superiority over other 5-HT<sub>3</sub> receptor antagonists has not been adequately demonstrated in the acute phase.

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Table 3: Prevention of Delayed Nausea and Vomiting (24-120 hours): Complete Response Rates

| Chemotherapy          | Study | Treatment Group      | N <sup>a</sup> | % with Complete Response | p-value <sup>b</sup> | 97.5% Confidence Interval ALOXI minus Comparator <sup>c</sup> |
|-----------------------|-------|----------------------|----------------|--------------------------|----------------------|---|
| Moderately Emetogenic | 1     | ALOXI 0.25 mg        | 189            | 74                       | <0.001               |   |
|                       |       | Ondansetron 32 mg IV | 185            | 55                       |                      |   |
|                       | 2     | ALOXI 0.25 mg        | 189            | 54                       | 0.004                |   |
|                       |       | Dolasetron 100 mg IV | 191            | 39                       |                      |   |

a Intent-to-treat cohort

b 2-sided Fisher's exact test. Significance level at  $\alpha=0.025$ .

c These studies were designed to show non-inferiority. A lower bound greater than -15% demonstrates non-inferiority between ALOXI and comparator.

These studies show that ALOXI was effective in the prevention of delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic chemotherapy.

Table 4: Prevention of Overall Nausea and Vomiting (0-120 hours): Complete Response Rates

| Chemotherapy          | Study | Treatment Group      | N <sup>a</sup> | % with Complete Response | p-value <sup>b</sup> | 97.5% Confidence Interval ALOXI minus Comparator <sup>c</sup> |
|-----------------------|-------|----------------------|----------------|--------------------------|----------------------|---|
| Moderately Emetogenic | 1     | ALOXI 0.25 mg        | 189            | 69                       | <0.001               |   |
|                       |       | Ondansetron 32 mg IV | 185            | 50                       |                      |   |
|                       | 2     | ALOXI 0.25 mg        | 189            | 46                       | 0.021                |   |
|                       |       | Dolasetron 100 mg IV | 191            | 34                       |                      |   |

a Intent-to-treat cohort

b 2-sided Fisher's exact test. Significance level at  $\alpha=0.025$ .

c These studies were designed to show non-inferiority. A lower bound greater than -15% demonstrates non-inferiority between ALOXI and comparator.

These studies show that ALOXI was effective in the prevention of nausea and vomiting throughout the 120 hours (5 days) following initial and repeat courses of moderately emetogenic cancer chemotherapy.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

NDC # 58063-797-25, 0.25 mg/5 mL (free base) single-use vial individually packaged in a carton

### Storage

- Store at controlled temperature of 20–25°C (68°F–77°F). Excursions permitted to 15–30 °C (59–86°F).
- Protect from freezing.
- Protect from light.

## 17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (17.2)

### 17.1 Instructions for Patients

- Patients should be advised to report to their physician all of their medical conditions, especially if they have heart problems including a problem called “congenital QT syndrome” or they are taking medicines that have caused or may cause severe heart beat changes such as diuretics, anti-arrhythmics or anthracycline. [see *Warnings and Precautions* (5.2)].
- Patients should be advised to report to their physician any pain, redness, or swelling in and around the infusion site [see *Adverse Reactions* (6.2)].
- Patients should be instructed to read the patient insert.

### 17.2 FDA-Approved Patient Labeling

## 17.2 FDA-Approved Patient Labeling

### Patient Information

## **ALOXI™ (Ah-lock-see)**

Palonosetron HCl injection

Read the Patient Information that comes with ALOXI before your treatment with ALOXI and each time you get ALOXI. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment. If you have questions about ALOXI, ask your doctor or pharmacist.

### **What is ALOXI?**

ALOXI is a medicine called an “antiemetic.” ALOXI is used in adults to help prevent the nausea and vomiting that happens:

- right away *with certain anti-cancer medicines (chemotherapy)*
- or later with certain anti-cancer medicines

### **What is ALOXI used for?**

ALOXI is used to prevent nausea and vomiting that may happen:

- soon after taking certain anti-cancer medicines
- later after taking certain anti-cancer medicines

### **Who should not take ALOXI?**

**Do not take ALOXI if you are allergic to any of the ingredients in ALOXI.** The active ingredient is palonosetron hydrochloride. See the end of this leaflet for a complete list of ingredients in ALOXI.

ALOXI has not been studied in children under 18 years of age.

### **What should I tell my doctor before using ALOXI?**

**Tell your doctor about all of your medical conditions, including if you:**

- **have heart problems** including a problem called “congenital QT syndrome”
- **have low potassium in your blood**
- **have low magnesium in your blood**
- **are pregnant.** It is not known if ALOXI may harm your unborn baby. You and your doctor should decide if ALOXI is right for you.
- **are breastfeeding.** It is not known if ALOXI passes into your milk and if it can harm your baby. You should choose to either take ALOXI or breastfeed, but not both.

**Tell your doctor about all of the medicines you take including prescription and nonprescription medicines, vitamins and herbal supplements.** ALOXI should be given with caution in patients who may be taking other medicines that have caused, or may cause, severe heart beat changes.

Especially, tell your doctor if you take:

- “water pills” (diuretics)
- medicine to control your heartbeat (anti-arrhythmics)
- anthracycline (an anti-cancer medicine)

### **How should I use ALOXI?**

ALOXI is given in your vein by IV (intravenous) injection. It is only given to you by a healthcare provider in a hospital or clinic. ALOXI is usually injected into your vein about 30 minutes before you get your anti-cancer medicine (chemotherapy).

## **What are the possible side effects of ALOXI?**

ALOXI should be given with caution in patients who have or may develop severe heart beat changes from QT prolongation. This can happen in people who have certain heart or other medical problems or who take certain medicines.

**The most common side effects of ALOXI are** headache and constipation. Diarrhea and dizziness have also been observed.

These are not all the side effects from ALOXI. For more information ask your doctor or pharmacist.

## **General information about ALOXI**

Medicines are sometimes prescribed for conditions other than those listed in patient information leaflets. ALOXI was prescribed for your medical condition.

This leaflet summarizes the most important information about ALOXI. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about ALOXI that is written for health professionals. You can also visit the ALOXI web site at [www.ALOXI.com](http://www.ALOXI.com). Or visit [www.ManageCINV.com](http://www.ManageCINV.com). This is a web site for patients with nausea and vomiting from anti-cancer medicines.

## **What are the ingredients in ALOXI?**

Active ingredient: palonosetron hydrochloride

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

### **Rx Only**

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