



New Drug Update

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Aloxi® (palonosetron HCl injection)

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Introduction

Aloxi® [palonosetron, (pal-oh-NOE-se-tron)] is an antiemetic and antinauseant agent that selectively blocks serotonin 5-HT₃ receptors. Palonosetron received FDA approval on July 25, 2003 and is indicated for the prevention of acute (within 24 hours) nausea and vomiting associated with initial and repeat courses of moderately and highly emetogenic cancer chemotherapy. Palonosetron is the first 5-HT₃ receptor antagonist indicated for the prevention of delayed (2-5 days) chemotherapy-induced nausea and vomiting caused by initial and repeat courses of moderately emetogenic cancer chemotherapy.

Therapeutic Recommendation

Palonosetron is approved for the prevention of acute nausea and vomiting following moderately and highly emetogenic cancer Chemotherapy, and is the first 5-HT₃ receptor antagonist approved for the prevention of

delayed nausea and vomiting following moderately emetogenic cancer chemotherapy. Palonosetron is effective for initial and repeat courses of chemotherapy with approximately a 100-fold stronger binding affinity for the 5-HT₃ receptor than other agents in the class. Slow elimination and an extended half-life of roughly 40 hours provides palonosetron with the clinical advantage of a single dose regimen that is effective for up to 5 days. Palonosetron demonstrated comparable efficacy to dolasetron when monitoring complete response during a 24 hour period as a primary endpoint in a phase III clinical trial (63.0% vs. 52.9%, respectively). Complete response was defined as no emetic episode and no use of rescue medication. Complete response rates during the delayed period (24 to 120 hours after chemotherapy) favored palonosetron over dolasetron and was measured as a secondary endpoint. Palonosetron does not have an oral dosage form available as do the other 5-HT₃ receptor antagonists currently on the market.

Dosing and Administration

The recommended dose of palonosetron is 0.25 mg infused intravenously over 30 seconds as a single dose 30 minutes before the start of chemotherapy. The infusion line should be flushed with normal saline before and after palonosetron administration. Palonosetron should not be mixed with other drugs. Doses of palonosetron should not be repeated in less than 7 days due to the long half-life of the drug.

In This Issue:

◆ Aloxi® (palonosetron HCl Injection)

◆ Ertaczo® (sertaconazole nitrate)

Precautions

Use caution in patients with a current or past history of prolonged cardiac conduction intervals (QT prolongation), arrhythmias, electrolyte imbalance, or dehydration. Palonosetron can block ion channels involved in ventricular de- and re-polarization and prolong action potential duration. Potassium levels should be within the normal range before and during palonosetron administration.

Contraindications

Palonosetron is contraindicated in patients with a known hypersensitivity to palonosetron or any of the inactive ingredients of the product. Use caution in patients allergic to other 5-HT₃ receptor antagonists; cross-sensitivity may exist.

Drug Interactions


No clinically significant drug interactions have been reported with palonosetron. Palonosetron is metabolized primarily by CYP2D6 and to a lesser extent CYP3A4 and CYP1A2. There are no differences between poor and extensive metabolizers of CYP2D6. Palonosetron does not inhibit or induce most of the metabolic enzymes, decreasing the potential for drug-drug interactions.

Use caution when administering palonosetron with other medications that may prolong the QT interval or cause arrhythmias. Examples include: Class IA antiarrhythmics, Class III antiarrhythmics, cardiac glycosides, cumulative high-dose anthracyclines, phenothiazines, and tricyclic antidepressants. Electrolyte abnormalities may also lead to cardiac dysrhythmias or QT prolongation. Hypokalemia and hypomagnesemia should be monitored with the use of loop and thiazide diuretics to avoid electrolyte imbalances.

Common Adverse Effects

The incidence and severity of adverse effects were similar between patients receiving palonosetron and those receiving placebo. The most common adverse effects reported in clinical trials with palonosetron are headache and constipation. Rates of adverse effects with palonosetron vs. ondansetron vs. dolasetron are: headache (9% vs. 8% vs. 16%), constipation (5% vs. 2% vs. 6%), and diarrhea (1% vs. 2% vs. 2%).

Other adverse effects occurring in ≤1% of patients included: abdominal pain, diarrhea, non-sustained tachycardia, sinus bradycardia, hypotension, hypertension, hyperkalemia, anxiety, dizziness, weakness, and dermatologic reactions. Frequency and severity of adverse effects were similar to patients treated with other 5-HT₃ receptor antagonists. Frequencies of adverse effects associated with palonosetron do not appear to be dose-related.



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Cost Comparison

Medication/Dose	Cost*		
	RiteAid	CVS	K-Mart
Aloxi® (palonosetron) 0.05 mg/mL solution 0.25 mg/5mL vial NDC: 58063-0797-25	372.99	359.99	322.97
Anzemet® (dolasetron) 100 mg/5mL solution 20mg/mL (5mL vial) NDC: 00088-1206-32	216.99	204.99	379.97
Zofran® (ondansetron) 32 mg/50mL injection 32 mg/50mL premixed bag NDC: 00173-0461-00	259.99	250.99	223.97
Kytril® (granisetron) 1 mg/mL solution 1 mg/mL vial NDC: 00004-0239-09	239.99	227.99	200.97

*Cost to the patient for 1 dose of medication. No generics are currently available for any of these products.

Special populations

- **Hepatic Impairment:** Dosage adjustments are not required.
- **Renal Impairment:** Dosage adjustments are not required.
- **Pediatrics:** Safety and efficacy of palonosetron has not been studied in children < 18 years of age.
- **Geriatrics:** Dosage adjustments are not required in the geriatric population.
- **Pregnancy:** Palonosetron is pregnancy category B. There are no adequate or well-controlled studies in pregnant women, and animal data often does not correlate with human response. Palonosetron should only be used in pregnant women if the benefits to the mother and fetus clearly outweigh the risks.
- **Lactation:** It is not known if palonosetron is excreted in human milk. Based on the importance of the drug to the mother, a decision should be made to discontinue the drug or discontinue nursing.
- **Dialysis:** It is unlikely that palonosetron is removed by dialysis due to the large volume of distribution. However, no dialysis studies have been performed.
- **Race:** Total body clearance was found to be somewhat higher in Japanese subjects compared to Caucasians, but no dosage adjustments are required. Palonosetron has not been adequately studied in African-Americans.

Pharmacology

Mechanism of Action

Palonosetron prevents emesis by selectively blocking 5-HT₃ receptors with little to no affinity for other serotonin receptors. 5-HT₃ receptors are located centrally in the chemoreceptor trigger zone (CTZ) of the area postrema and peripherally on nerve terminals of the vagus in the intestines. Chemotherapeutic agents produce nausea and vomiting by releasing serotonin from enterochromaffin cells in the small intestine. The serotonin

released initiates the vomiting reflex by activating 5-HT₃ receptors on vagal afferent nerves.

Absorption/Distribution

Palonosetron is administered by intravenous infusion. Plasma concentrations initially rise and are followed by a slow elimination from the body in both healthy subjects and cancer patients. Palonosetron is approximately 62% bound to plasma proteins. The volume of distribution is large at 8.3 +/- 2.5 L/kg.

Metabolism/Excretion

Palonosetron is metabolized primarily by CYP2D6 and to a lesser extent CYP3A4 and CYP1A2. Approximately 50% of the dose is metabolized to two inactive metabolites, N-oxide-palonosetron and 6-S-hydroxy-palonosetron. After a single IV dose of palonosetron, approximately 80% of the dose was recovered in the urine within 144 hours. The parent drug accounted for roughly 40% of the administered dose. Total body clearance and renal clearance of palonosetron in healthy subjects are 160 +/- 35 mL/h/kg and 66.5 +/- 18.2 mL/h/kg respectively. Palonosetron has a long half-life of approximately 40 hours.

Patient Information

- Patients should inform their doctor/prescriber of all medications they are currently taking including: all prescriptions, over-the-counter medications, vitamins, or herbal supplements.
- Palonosetron may cause dizziness or drowsiness.
- Patients should use caution when driving or performing activities that require alertness until they know how they will be affected by this medication.
- Patients should report persistent headaches, excessive drowsiness, constipation, diarrhea, or chest pain to their doctor.
- Patients should inform their doctor if they are allergic to any medications, are pregnant, or are planning to become pregnant.
- Patients should ask a doctor or pharmacist before taking any new medications or over-the-counter remedies.

References

1. Aloxi® (palonosetron HCl injection) prescribing information, MGI Pharma Inc and Helsinn Healthcare. Bloomington, MN, September 2004.
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Ertaczo® (sertaconazole nitrate) cream, 2%

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Introduction

Ertaczo® [sertaconazole, (ser-ta-KOE-na-zole)] is an imidazole antifungal cream for the treatment of interdigital tinea pedis in immunocompetent patients, approved by the FDA in December 2003. Sertaconazole cream, 2%, is comprised of 17.5 mg of sertaconazole per gram in a cream base. Sertaconazole is active against *Trichophyton rubrum*, *Trichophyton mentagrophytes*, and *Epidermophyton floccosum*.

Therapeutic Recommendation

Sertaconazole is one of various topical antifungals available by prescription, including

Mentax® (butenafine), Spectazole® econazole), Exelderm® (sulconazole), Oxistat® (oxiconazole), and Naftin® (naftifine). Sertaconazole has been shown to be significantly more effective in treating fungal infections than placebo vehicle cream with minimal adverse effects. It has also been shown to be safe and effective at treating tinea pedis over a three week treatment period with twice daily application. Efficacy and duration of treatment appear to be similar among the various topical antifungals available by prescription. Importantly, several of the non-prescription antifungals (such as butenafine and terbinafine) require only one week of therapy for tinea pedis versus four weeks with sertaconazole. There does not appear to be any noteworthy advantage of sertaconazole over any other the other antifungals, some of which are available as generic and/or over-the-counter products.

Dosing and Administration

Sertaconazole is available in as a 2% cream in 15 and 30 gram tubes. To treat interdigital tinea pedis, sertaconazole 2% cream should be applied to the affected area and the nearby, unaffected skin two times a day for 4 weeks. Improvement is usually seen within 2 weeks, but treatment should be continued for the entire recommended time period.

Contraindications

Sertaconazole cream, 2%, should not be used in patients who are hypersensitive to sertaconazole nitrate, to other imidazoles, or to any component used in the cream base.

Drug Interactions

Evaluations of potential drug-drug interactions with sertaconazole have not been performed. In general, imidazoles are not typically used with amphotericin B and nystatin. Imidazoles can reduce the number of polyene binding sites which both amphotericin B and nystatin need to have an effect. However, some clinicians choose to use imidazole with either amphotericin B or nystatin in certain patients.

Common Adverse Drug Reactions

During clinical studies, adverse events were reported in 7 of 297 patients receiving sertaconazole.

zole and 7 of 291 patients receiving placebo vehicle. The reported events included contact dermatitis, skin hyperpigmentation, erythematous site reaction, and dry and burning skin.

Special populations

- **Pediatrics:** Sertaconazole cream, 2%, has not been evaluated in and is not approved for children less than 12 years of age.
- **Geriatrics:** Inadequate numbers of elderly patients have been included in clinical trials to conclude if patients over 65 years of age will respond in the same way as other adult patients, but these patients would be expected to respond similarly to younger adult patients.
- **Pregnancy:** Sertaconazole cream, 2%, is considered pregnancy category C. Clinical studies in mice did not result in any teratogenic effects. However, adequate trials in humans have not been conducted. Sertaconazole should be used in pregnancy only if there is a clear need.
- **Lactation:** Since sertaconazole is a topical product, it would not be expected to be secreted in breast milk. However, data concerning this does not exist. Sertaconazole cream, 2%, should be used cautiously in nursing mothers.

Cost Comparison

Medication/Dose	Cost [^]		
	RiteAid	Kroger	CVS
Mentax® (butenafine)	84.99	86.89	94.99
Spectazole® (econazole)	48.99	59.59	50.99
Generic econazole	38.99	43.49	41.29
Exelderm® (sulconazole)	35.99	34.59	31.19
Oxistat® (oxiconazole)	54.99	59.39	54.59
Naftin® (naftifine)	65.99	67.89	58.59
Eraczo® (sertaconazole)	60.99	56.99	61.99
Lotrimin AF® (clotrimazole) [OTC] ⁺	9.99	8.99	9.99
Lamisil AT® (terbinafine) [OTC] ⁺	8.99	9.99	9.99
Tinactin® (tolnaftate) [OTC] [◆]	7.49	6.99	7.69

[^] Cost based on 30 gm tube of each cream (prescription products only).

⁺ Cost based on 12 gm tube

[◆] Cost based on 15 gm tube

Pharmacology

Mechanism of Action

Sertaconazole belongs to the imidazole antifungal class of medication. The mechanism of action of sertaconazole is not completely known.

Sertaconazole apparently inhibits ergosterol synthesis through the cytochrome P-450 system. The cell membrane of fungi contain ergosterol. Without ergosterol synthesis, the cell membrane of fungi are compromised resulting in fungal cell leakage and death.

Pharmacokinetics

Sertaconazole cream, 2%, does not appear to be absorbed into the systemic circulation to any appreciable extent. In a pharmacokinetic study, plasma levels of sertaconazole were undetectable by the analytical method used after the thirteenth application of sertaconazole cream, 2% applied every 12 hours. The metabolism and elimination of sertaconazole are unknown.

Patient Information

- Do not use sertaconazole cream, 2% if you are allergic to any azole antifungal or any component of the preparation.
- Inform your physician or pharmacist if you have diabetes mellitus, are immunocompromised, have had any kind of reaction to azole antifungals, are pregnant, or are breast-feeding.
- Sertaconazole cream, 2%, is for external use only. Apply only to affected areas of the skin and the healthy skin surrounding the affected areas. Avoid contact with eyes, nose, mouth, and mucous membranes.
- Be sure that the affected areas of the skin are dry before applying. Wash your hands immediately following application.
- Use sertaconazole cream, 2%, for the entire time prescribed by your physician even if your symptoms improve. If your condition becomes worse or there is no improvement by the end of the treatment period, notify your physician.
- If you experience burning, itching, swelling, redness, or increased irritation, notify your

physician.

- Do not apply occlusive dressings to the affected area unless your physician directs you to do otherwise.
- Do not use sertaconazole cream, 2 %, for any condition other than the one for which it was prescribed.

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Page 6



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