Paloxiron®

Palonosetron Hydrochloride

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PRESENTATION

Paloxiron® 5: Each 5 ml ampoule contains 0.25 mg of Palonosetron as Palonosetron Hydrochloride INN.
Paloxiron®1.5: Each 1.5 ml ampoule contains 0.075 mg of Palonosetron as Palonosetron Hydrochloride INN.
Paloxiron®: Each tablet contains 0.5 mg of Palonosetron as Palonosetron Hydrochloride INN.

PHARMACOKINETICS

Absorption

Following IV administration, the C_{max} and AUC are generally dose-proportional. After a single IV dose at 3 mcg/kg, mean C_{max} was approximately 5.6 ng/mL and AUC was 35.8 ng-h/mL.

Distribution

Vd is approximately 8.3 L/kg, and protein binding is about 62%.

Metabolism

Approximately 50% is metabolized to 2 metabolites that have less than 1% of the activity of Palonosetron. The major isozyme responsible for metabolism appears to be CYP2D6 and, to a lesser degree, CYP1A2 and CYP3A are involved.

Elimination

Following IV administration, approximately 80% of the dose is recovered in the urine. The terminal half-life is approximately 40 h.

PHARMACODYNAMICS

The effect of Palonosetron on blood pressure, heart rate, and ECG parameters including QTc were comparable to ondansetron and dolasetron in CINV clinical trials. In PONV clinical trials the effect of Palonosetron on the QTc interval was no different from placebo.

MECHANISM OF ACTION

Cancer chemotherapy may be associated with a high incidence of nausea and vomiting. 5-HT_3 receptors are located on the nerve terminals of the vagus in the periphery and centrally in the chemoreceptor trigger zone. It is thought that chemotherapeutic agents release serotonin (5-HT) from the enterochromaffin cells of the small intestine. The released serotonin then activates 5-HT_3 receptors located on vagal afferents to initiate the vomiting reflex. Postoperative nausea and vomiting is influenced by multiple patient, surgical and anesthesia related factors and is triggered by release of serotonin (5-HT) in a cascade of neuronal events involving both the central nervous system and the gastrointestinal tract. The 5-HT_3 receptor has been demonstrated to selectively participate in the emetic response. Palonosetron is a 5-HT_3 receptor antagonist with a strong binding affinity for this receptor. As a result, serotonin can't activates 5-HT_3 receptors and thus fails to initiate vomiting reflux.

INDICATIONS

- 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
- Prevention of postoperative nausea and vomiting (PONV) for up to 24 hours following surgery. Efficacy beyond 24 hours has not been demonstrated

DOSAGE AND ADMINISTRATION

Injection

Chemotherapy Induced Nausea and Vomiting

Dosage for pediatrics (1 month to less than 17 years) - A single dose of 20 micrograms per kilogram (maximum 1.5 mg) administered over 15 minutes. Dosing should occur approximately 30 minutes before the start of chemotherapy.
Dosage for Adults - A single 0.25 mg I.V. dose administered over 30 seconds. Dosing should occur 30 minutes before the start of chemotherapy.

Postoperative Nausea and Vomiting

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

Tablet

Chemotherapy Induced Nausea and Vomiting

0.5 mg tablet should be taken approximately 1 hour before the start of chemotherapy.

GENERAL ADVICE

- For IV administration only. Not for intradermal, subcutaneous, or IM administration.
- Do not administer if particulate matter, cloudiness, or discoloration is noted.
- Discard any unused solution. Do not store unused solution for later administration.
- Do not mix with other medications.

CONTRAINDICATION AND PRECAUTION

Palonosetron is contraindicated in patients known to have hypersensitivity to the drug or any of its components.
Hypersensitivity reactions may occur in patients who have exhibited hypersensitivity to other selective 5-HT3 receptor antagonists.

SIDE EFFECTS

The most common adverse reactions in chemotherapy-induced nausea and vomiting (incidence ≥5%) are headache and constipation. The most common adverse reactions in postoperative nausea and vomiting (incidence ≥2%) are QT prolongation, bradycardia, headache, and constipation.

DRUG INTERACTION

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, drug interactions with Paloxiron appears to be low. In controlled clinical trials, Palonosetron injection has been safely administered with corticosteroids, analgesics, antiemetics/antinauseants, antispasmodics and anticholinergic drugs. Palonosetron did not inhibit the antitumor activity of the five chemotherapeutic agents tested (cisplatin, cytarabine, doxorubicin and mitomycin C) in murine tumor models.

USE IN PREGNANCY AND LACTATION

Pregnancy category B. It is not known whether Palonosetron is excreted in human milk.

PEDIATRIC USE

Safety and effectiveness in patients below the age of 18 years have not been established. However different clinical trial shows Palonosetron is well tolerated and effective from one month of age.

GERIATRIC USE

Pharmacokinetics analysis did not reveal any differences in Palonosetron pharmacokinetics between patients of 65 years of age and younger patients (18 to 64 years).

USE IN SPECIAL CASES

Renal Function Impairment : No dosage adjustments are needed with any degree of renal function impairment.
Hepatic Function Impairment : No dosage adjustments are needed with any degree of hepatic function impairment. Elderly : No dosage adjustments or special monitoring are needed in elderly patients.

STORAGE CONDITION

Store at controlled temperature of 20-25°C (68°F-77°F). Protect from light and protect injectable from freezing.

COMMERCIAL PACK

Paloxiron®5: Each box contains 1 ampoules of 5 ml solution for IV injection.
Paloxiron®1.5: Each box contains 1 ampoules of 1.5 ml solution for IV injection.
Paloxiron®: Each box contains 1 blister strip of 10 tablets.

Manufactured by
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