Ondax

(Ondansetron)

8mg Orally Disintegrating Tablets U.S.P.

8mg/4mL Injection U.S.P.

QUALITATIVE AND QUANTITATIVE COMPOSITION

Ondax Orally Disintegrating Tablets U.S.P. 8mg:
Each orally disintegrating tablet contains: Ondansetron Hydrochloride Dihydrate U.S.P. eq. to Ondansetron.....8mg

Ondax Injection U.S.P. 8mg/4mL:
Each 4mL ampoule contains: Ondansetron Hydrochloride Dihydrate U.S.P. eq. to Ondansetron.....8mg

DESCRIPTION

Ondax tablets and injection contains a medicine called ondansetron (as hydrochloride dihydrate). Ondax is indicated for the prevention of nausea and vomiting associated with: • highly emetogenic cancer chemotherapy, including cisplatin greater than or equal to 50mg/m2. • initial and repeat courses of moderately emetogenic cancer chemotherapy. • radiotherapy in patients receiving either total body irradiation, single high-dose fraction to the abdomen or daily fractions to the abdomen

CLINICAL PHARMACOLOGY

Mechanism of Action: Ondansetron is a selective 5-HT3 receptor antagonist. While its mechanism of action has not been fully characterized, ondansetron is not a dopamine-receptor antagonist. Serotonin receptors of the 5-HT3 type are present both peripherally on vagal nerve terminals and centrally in the chemoreceptor trigger zone of the area postrema. It is not certain whether ondansetron's antiemetic action is mediated centrally, peripheral-ly, or in both sites. However, cytotoxic chemotherapy appears to be associated with release of serotonin from the enterochromaffin cells of the small intestine. In humans, urinary 5-hydroxyindoleacetic acid (5-HIAA) excretion increases after cisplatin administration in parallel with the onset of emesis. The released seroto-nin may stimulate the vagal afferents through the 5-HT3 receptors and initiate the vomiting reflex.

Pharmacokinetics: Absorption: Ondansetron is passively and completely absorbed from the gastrointestinal tract and under-goes first pass metabolism (Bioavailability is about 60%.). Peak plasma concentrations of about 30 ng/ml are attained approximately 1.5 hours after an 8 mg dose. For doses above 8 mg the increase in ondansetron systemic exposure with dose is greater than proportional; this may reflect some reduction in first pass me-tabolism at higher oral doses. Bioavailability, following oral administration, is slightly enhanced by the presence of food but unaffected by antacids. A 4 mg intravenous infusion of ondansetron given over 5 minutes' results in peak plasma concentrations of about 65 ng/ml. Following intramuscular administration of ondansetron, peak plasma concentrations of about 25 ng/ml are attained within 10 minutes of injection.

Distribution: The disposition of ondansetron following oral, intramuscular (IM) and intravenous (IV) dosing is similar with a steady state volume of distribution of about 140 L. Equivalent systemic exposure is achieved after IM and IV administration of ondansetron. Ondansetron is not highly protein bound (70-76%).

Metabolism: Ondansetron is cleared from the systemic circulation predominantly by hepatic metabolism through multiple enzymatic pathways. The absence of the enzyme CYP2D6 (the debrisoquine polymor-phism) has no effect on ondansetron's pharmacokinetics.

Excretion: Less than 5% of the absorbed dose is excreted unchanged in the urine. Terminal half-life is about 3 hours.

INDICATIONS: Adults: Ondansetron is indicated for the prevention and treatment of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy, and for the prevention and treatment of postoperative nausea and vomiting (PONV).

Paediatric Population: Ondansetron is indicated for the management of chemotherapy-induced nausea and vomiting (CINV) in children aged ≥6 months, and for the prevention and treatment of PONV in children aged ≥1 month.

CONTRAINDICATIONS

Concomitant use with apomorphine. Hypersensitivity to any component of the preparation.

INTERACTIONS

Effects of ondansetron on other medicinal products: There is no evidence that ondansetron either induces or inhibits the metabolism of other drugs commonly coadministered with it. Specific studies have shown that ondansetron does not interact with alcohol, temazepam, furosemide, alfentanil, morphine, lignocaine, propofol and thiopental.

Effects of other medicinal products on ondansetron: Ondansetron is metabolised by multiple hepatic cytochrome P-450 enzymes: CYP3A4, CYP2D6 and CYP1A2. Due to the multiplicity of metabolic enzymes capable of metabolising ondansetron, enzyme inhibition or reduced activity of one enzyme (e. g. CYP2D6 genetic deficiency) is normally compensated by other enzymes and should result in little or no significant change in overall ondansetron clearance or dose requirement. Use of ondansetron with QT prolonging drugs may result in additional QT prolongation. Concomitant use of ondansetron with cardiotoxic drugs (e.g. anthracyclines such as doxorubicin, daunorubicin or trastuzimab), antibiotics (such as erythromycin or ketoconazole), antiarrhythmics (such as amiodarone) and beta blockers (such as atenolol or timolol) may increase the risk of arrhythmias

Phenytoin, carbamazepine and rifampicin: In patients treated with potent inducers of CYP3A4 (i. e. phenyto-in, carbamaze-pine and rifampicin), the oral clearance of ondansetron was increased and ondansetron blood concentrations were decreased.

USE IN SPECIFIC POPULATION

Women of childbearing potential: Women of childbearing potential should consider the use of contraception.

Pregnancy: Ondansetron is suspected to cause orofacial malformations when administered during the first trimester of pregnancy.

Lactation: It is therefore recommended that mothers receiving ondansetron should not breast-feed their babies.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hypersensitivity reactions have been reported in patients who have exhibited hypersensitivity to other selective 5-HT3 receptor antagonists. Respiratory events should be treated symptomatically and clinicians should pay particular attention to them as precursors of hypersensitivity reactions.

Hypokalaemia hypomagnesaemia should be corrected prior to ondansetron administration.

Paediatric Population: Paediatric patients receiving ondansetron with hepatotoxic chemotherapeutic agents should be monitored closely for impaired hepatic function.

ADVERSE REACTIONS

Common: Headache, Sensations of flushing or warmth, Ondansetron is known to increase the large bowel transit time and may cause constipation in some patients.

Uncommon: There have been reports suggestive of involuntary movement disorders such as extrapyramidal reactions, Chest pain with or without ST segment depression, cardiac arrhythmias and bradycardia. Chest pain and cardiac arrhythmias may be fatal in individual cases, Hypotension, Hiccups, Asymptomatic increases in liver function tests were observed. These reactions were frequently observed in patients under chemotherapy with cisplatin, Hypersensitivity reactions around the injection site (e.g. rash, urticaria, itching) may occur, sometimes extending along the drug administration vein.

DOSAGE AND ADMINISTRATION

The recommended dosage regimens for adult and pediatric patients are described in Table 1 and Table 2, respectively.

Table 1: Adult Recommended Dosage Regimen for Prevention of Nausea and Vomiting

Indication	Dosage Regimen
Highly Emetogenic Cancer Chemotherapy	A single 24-mg dose administered 30 minutes before the start of single-day highly emetogenic chemotherapy, including cisplatin greater than or equal to 50 mg/m2
Moderately Emetogenic Cancer Chemotherapy	8 mg administered 30 minutes before the start of chemotherapy, with a subsequent 8-mg dose 8 hours after the first dose. Then administer 8 mg twice a day (every 12 hours) for 1 to 2 days after completion of chemotherapy.
Radiotherapy	For total body irradiation: 8 mg administered 1 to 2 hours before each fraction of radiotherapy each day. For single high-dose fraction radiotherapy to the abdomen: 8 mg administered 1 to 2 hours before radiotherapy, with subsequent 8-mg doses every 8 hours after the first dose for 1 to 2 days after completion of radiotherapy. For daily fractionated radiotherapy to the abdomen: 8 mg administered 1 to 2 hours before radiotherapy, with subsequent 8-mg doses every 8 hours after the first dose for each day radiotherapy is given.
Postoperative	16 mg administered 1 hour before induction of anesthesia.

Table 2: Pediatric Recommended Dosage Regimen for Prevention of Nausea and Vomiting

Indication	Dosage Regimen
Moderately Emetogenic Cancer Chemotherapy	**12 to 17 years of age:** 8 mg administered 30 minutes before the start of chemotherapy, with a subsequent 8-mg dose 4 and 8 hours after the first dose. Then administer 8 mg three times a day for 1 to 2 days after completion of chemotherapy. **4 to 11 years of age:** 4 mg administered 30 minutes before the start of chemotherapy, with a subsequent 4-mg dose 4 and 8 hours after the first dose. Then administer 4 mg three times a day for 1 to 2 days after completion of chemotherapy.

INSTRUCTIONS

Dosage as directed by the physician.
To be sold on the prescription of a registered medical practitioner only.
Tablets: Store below 30°C. Protect from heat, light and moisture.
Injection: Store between 2°C to 30°C. Protect from light.
Keep all medicines out of the reach of children.

PRESENTATION

Ondax (Ondansetron Hydrochloride Dihydrate) Tablets U.S.P. 8mg are available in Alu-Alu blister pack of 1x10's with leaf insert.
Ondax (Ondansetron Hydrochloride Dihydrate) Injection U.S.P. 8mg/4mL is available in 4mL x 5's glass ampoule with leaf insert.

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