Onseget™

[O n d a n s e t r o n]

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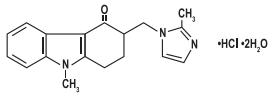
Film-coated Tablets 8mg

DESCRIPTION

Onseget (Ondansetron) is the racemic form of ondansetron and a selective blocking agent of the serotonin 5-HT_3 receptor type. Chemically it is (±) 1, 2, 3, 9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4Hcarbazol- 4-one, monohydrochloride, dihydrate. Its molecular formula is $C_{18}H_{19}N_3O$•HCl •$2H_2O$ and the structural formula is:



Ondansetron Hydrochloride Dihydrate

QUALITATIVE AND QUANTITATIVE COMPOSITION

Onseget (Ondansetron) Tablets are available for oral administration as:

Onseget Tablets 8mg
Each film-coated tablet contains:
Ondansetron Hydrochloride (as Dihydrate) USP equivalent to Ondansetron… 8mg

CLINICAL PHARMACOLOGY

Mechanism of action

Ondansetron is a potent, highly selective $5HT_3$ receptor-antagonist. Its precise mode of action in the control of nausea and vomiting is not known. Chemotherapeutic agents and radiotherapy may cause release of 5HT in the small intestine initiating a vomiting reflex by activating vagal afferents via $5HT_3$ receptors. Ondansetron blocks the initiation of this reflex. Activation of vagal afferents may also cause a release of 5HT in the area postrema, located on the floor of the fourth ventricle, and this may also promote emesis through a central mechanism. Thus, the effect of ondansetron in the management of the nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy is probably due to antagonism of $5HT_3$ receptors on neurons located both in the peripheral and central nervous system. The mechanisms of action in post-operative nausea and vomiting are not known but there may be common pathways with cytotoxic induced nausea and vomiting.

Pharmacokinetics

Absorption

Following oral administration, ondansetron is passively and completely absorbed from the gastrointestinal tract. Peak plasma concentrations of about 30ng/ml are attained approximately1.5 hours after an 8mg dose. For doses above 8mg the increase in ondansetron systemic exposure with dose is greater than proportional; this may reflect some reduction in first pass metabolism at higher oral doses. Bioavailability, following oral administration, is slightly enhanced by the presence of food but unaffected by antacids.

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 extensively metabolized in humans, with approximately 5% of a radiolabeled dose recovered as the parent compound from the urine. The primary metabolic pathway is hydroxylation on the indole ring followed by subsequent glucuronide or sulfate conjugation.
Ondansetron is cleared from the systemic circulation predominantly by hepatic metabolism through multiple enzymatic pathways. The absence of the enzyme CYP2D6 (the debrisoquine polymorphism) has no effect on ondansetron's pharmacokinetics.

Elimination

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

Special Populations

Elderly

A reduction in clearance and increase in elimination half-life are seen in patients older than 75 years of age. There is a slight age-related increases in both oral bioavailability (65%) and half-life (5 hours).

Renal impairment

Renal impairment is not expected to significantly influence the total clearance of ondansetron as renal clearance represents only 5% of the overall clearance. However, the mean plasma clearance of ondansetron was reduced by about 50% in patients with severe renal impairment (creatinine clearance less than 30 mL/min). The reduction in clearance was variable and not consistent with an increase in half-life.

Hepatic impairment

In patients with mild-to-moderate hepatic impairment, clearance is reduced 2-fold and mean half-life is increased to 11.6 hours compared with 5.7 hours in those without hepatic impairment. Following oral, intravenous or intramuscular dosing in patients with severe hepatic impairment, ondansetron's systemic clearance is markedly reduced with prolonged elimination half-lives (15-32 h) and an oral bioavailability approaching 100% due to reduced pre-systemic metabolism.

THERAPEUTIC INDICATIONS

Adults

Onseget (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 post-operative nausea and vomiting (PONV).

Pediatric Population

Onseget (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.

DOSAGE AND ADMINISTRATION

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

Chemotherapy and Radiotherapy induced nausea & vomiting

Adults

Indication	Dosage Regimen
Highly Emetogenic Cancer Chemotherapy	A single 24mg dose administered 30 minutes before the start of single-day highly emetogenic chemotherapy, including cisplatin greater than or equal to 50mg/m^2. To protect against delayed or prolonged emesis after the first 24 hours, oral treatment with ondansetron should be continued for up to 5 days after a course of treatment. The recommended dose for oral administration is 8mg twice daily.
Moderately Emetogenic Cancer Chemotherapy	8mg administered 30 minutes before the start of chemotherapy, with a subsequent 8mg dose 8 hours after the first dose. Then administer 8mg twice a day (every 12 hours) for 1 to 2 days after completion of chemotherapy.
Radiotherapy	For total body irradiation: 8mg administered 1 to 2 hours before each fraction of radiotherapy each day. For single high-dose fraction radiotherapy to the abdomen: 8mg administered 1 to 2 hours before radiotherapy, with subsequent 8mg doses every 8 hours after the first dose for 1 to 2 days after completion of radiotherapy. For daily fractionated radiotherapy to the abdomen: 8mg administered 1 to 2 hours before radiotherapy, with subsequent 8mg doses every 8 hours after the first dose for each day radiotherapy is given.

Pediatric Population

Indication	Dosage Regimen
Highly Emetogenic Cancer Chemotherapy	*Ages ≥6 months and adolescents:* Ondansetron should be administered immediately before chemotherapy as a single intravenous dose of 5 mg/m^2. The intravenous dose must not exceed 8mg. Oral dosing can commence twelve hours later and may be continued for up to 5 days. See table below. The total daily dose must not exceed adult dose of 32mg. *Table: BSA-based dosing for chemotherapy – Children aged ≥6 months and adolescents* BSA (body surface area) / Day1[a,b] / Days 2-6[b]: < 0.6m^2 — 5mg/m^2 IV, 2mg oral solution or tablet after 12 hours — 2mg oral solution or tablet every 12 hours > 0.6 m^2 — 5mg/m^2 IV, 4mg oral solution or tablet after 12 hours — 4mg oral solution or tablet every 12 hours [a] *The intravenous dose must not exceed 8mg* [b] *The total daily dose must not exceed adult dose of 32mg* *Dosing by body weight:* Ondansetron should be administered immediately before chemotherapy as a single intravenous dose of 0.15 mg/kg the intravenous dose must not exceed 8mg. Two further intravenous doses may be given in 4-hourly intervals. The total daily dose must not exceed adult dose of 32mg. Oral dosing can commence twelve hours later and may be continued for up to 5 days. See table below. *Table: Weight-based dosing for chemotherapy – children aged ≥6 months and adolescents* Weight / Day 1[a,b] / Days 2-6[b]: ≤ 10kg — Up to 3 doses of 0.15mg/kg at 4-hourly intervals. — 2mg oral solution or tablet every 12 hours > 10kg — Up to 3 doses of 0.15mg/kg at 4-hourly intervals. — 4mg oral solution or tablet every 12 hours [a] *The intravenous dose must not exceed 8mg* [b] *The total daily dose must not exceed adult dose of 32mg*
Moderately Emetogenic Cancer Chemotherapy	12 to 17 years of age: 8mg administered 30 minutes before the start of chemotherapy, with a subsequent 8mg dose 8 hours after the first dose. Then administer 8mg twice a day (every 12 hours) for 1 to 2 days after completion of chemotherapy. 4 to 11 years of age: 4mg administered 30 minutes before the start of chemotherapy, with a subsequent 4mg dose 4 and 8 hours after the first dose. Then administer 4mg three times a day for 1 to 2 days after completion of chemotherapy.

Postoperative nausea & vomiting (PONV)

Adults

Indication	Dosage Regimen
Postoperative	*For oral administration:* 16mg administered 1 hour before induction of anesthesia. Alternatively, 8mg one hour prior to anesthesia followed by two further doses of 8mg at eight hourly intervals. Treatment of established PONV **For the treatment of established PONV intravenous administration is recommended.**

Pediatric Population

Indication	Dosage Regimen
Postoperative	Ages ≥1 months and adolescents *For oral administration:* no studies have been conducted on the use of orally administer ondansetron in the prevention or treatment of PONV.

Special Populations
Patients with Hepatic Impairment
Clearance of ondansetron is significantly reduced and serum half-life significantly prolonged in subjects with moderate or severe impairment of hepatic function. In such patients, a total daily dose of 8mg should not be exceeded.

ADVERSE REACTIONS
Very Common: Headache.

Common: Sensations of flushing or warmth, increase large bowel transit time, constipation and local reactions at the IV injection site.

Uncommon: Extrapyramidal reactions, e.g. oculogyric crisis/dystonic reactions, dyskinesia, epileptic spasms, chest pain with or without ST segment depression, cardiac arrhythmias, bradycardia, hypotension, hiccups, asymptomatic increases in liver function tests and hypersensitivity reactions around the injection site (e.g. rash, urticaria, itching).

Rare: Immediate hypersensitivity reactions, anaphylaxis, dizziness during rapid intravenous administration, transient visual disturbances (e.g. blurred vision) during rapid intravenous administration, transitory changes in the electrocardiogram and QTc prolongation (including Torsades de Pointes).

Very Rare: Transitory blindness.

"To report SUSPECTED ADVERSE REACTIONS to Getz Pharma's pharmacovigilance Section, please contact at dsafety@getzpharma.com or +92-21-38636363"

CONTRAINDICATIONS
- Ondansetron is contraindicated in patients who are hypersensitive to the active substance or other pyrrolidone derivatives or to any the excipient of the product.
- The concomitant use of apomorphine with ondansetron is contraindicated based on reports of profound hypotension and loss of consciousness when apomorphine was administered with ondansetron.

PRECAUTIONS
- Hypersensitivity reactions, including anaphylaxis and bronchospasm, have been reported in patients who have exhibited hypersensitivity to other selective 5-HT_3 receptor antagonists.
- Ondansetron prolongs the QT interval in a dose-dependent manner. In addition, post marketing cases of Torsade de Pointes have been reported in patients using ondansetron. Avoid Ondansetron in patients with congenital long QT syndrome. Electrocardiogram (ECG) monitoring is recommended in patients with electrolyte abnormalities (e.g., hypokalemia or hypomagnesemia), congestive heart failure, bradyarrhythmias, or patients taking other medicinal products that lead to QT prolongation.
- Respiratory events should be treated symptomatically and clinicians should pay particular attention to them as precursors of hypersensitivity reactions.
- The development of serotonin syndrome has been reported with 5-HT_3 receptor antagonists. Most reports have been associated with concomitant use of serotonergic drugs (e.g., selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors, mirtazapine, fentanyl, lithium, tramadol, and intravenous methylene blue). Some of the reported cases were fatal. Serotonin syndrome occurring with overdose of Ondansetron alone has also been reported. The majority of reports of serotonin syndrome related to 5-HT_3 receptor antagonist use occurred in a post-anesthesia care unit or an infusion center.
- As ondansetron is known to increase large bowel transit time, patients with signs of subacute intestinal obstruction should be monitored following administration.
- In patients with adenotonsillar surgery prevention of nausea and vomiting with ondansetron may mask occult bleeding. Therefore, such patients should be followed carefully after ondansetron.
- Hypokalemia and hypomagnesemia should be corrected prior to ondansetron administration.
- The use of ondansetron in patients following abdominal surgery or in patients with chemotherapy-induced nausea and vomiting may mask a progressive ileus and/or gastric distension. Monitor for decreased bowel activity, particularly in patients with risk factors for gastrointestinal obstruction.
- This product contains lactose. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-glucose malabsorption should not take this medicine.
- Women of childbearing potential should consider the use of contraception.
- Pediatric patients receiving ondansetron with hepatotoxic chemotherapeutic agents should be monitored closely for impaired hepatic function.

Pregnancy
Ondansetron is suspected to cause orofacial malformations when administered during the first trimester of pregnancy. Ondansetron should not be used during first trimester of pregnancy.

Nursing Mothers
Ondansetron passes into the milk of lactating animals. It is therefore recommended that mothers receiving ondansetron should not breast-feed their babies.

DRUG INTERACTIONS
Drugs Affecting Cytochrome P-450 Enzymes
Ondansetron does not appear to induce or inhibit the cytochrome P-450 drug-metabolizing enzyme system of the liver. Because ondansetron is metabolized by hepatic cytochrome P-450 drug-metabolizing enzymes (CYP3A4, CYP2D6, CYP1A2), inducers or inhibitors of these enzymes may change the clearance and, hence, the half-life of ondansetron.

Phenytoin, Carbamazepine, and Rifampin
In patients treated with potent inducers of CYP3A4 (i.e., phenytoin, carbamazepine, and rifampin), the clearance of ondansetron was significantly increased and ondansetron blood concentrations were decreased.

Tramadol
Concomitant use of ondansetron may result in reduced analgesic activity of tramadol.

QT Prolongation
Caution should be exercised when ondansetron is coadministered with drugs that prolong the QT interval and/or cause electrolyte abnormalities. 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.

Serotonergic Drugs (e.g. SSRI's and SNRI's)
Serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) has been described following the concomitant use of ondansetron with other serotonergic drugs, including selective serotonin reuptake inhibitors (SSRI's) and serotonin noradrenaline reuptake inhibitors (SNRI's).

OVERDOSAGE
There is no specific antidote for ondansetron overdose. Patients should be managed with appropriate supportive therapy.

In addition to the adverse reactions listed above, the following adverse reactions have been described in the setting of ondansetron overdose: "Sudden blindness" (amaurosis) of 2 to 3 minutes duration plus severe constipation occurred in one patient that was administered 72mg of ondansetron intravenously as a single dose. Hypotension (and faintness) occurred in a patient that took 48mg of Ondansetron tablets. Following infusion of 32mg over only a 4-minute period, a vasovagal episode with transient second-degree heart block was observed. In all instances, the adverse reactions resolved completely.

Pediatric cases consistent with serotonin syndrome have been reported after inadvertent oral overdoses of ondansetron (exceeding estimated ingestion of 5mg per kg) in young children. Reported symptoms included somnolence, agitation, tachycardia, tachypnea, hypertension, flushing, mydriasis, diaphoresis, myoclonic movements, horizontal nystagmus, hyperreflexia, and seizure. Patients required supportive care, including intubation in some cases, with complete recovery without sequelae within 1 to 2 days.

The use of ipecacuanha to treat overdose with ondansetron is not recommended, as patients are unlikely to respond due to the anti-emetic action of ondansetron itself.

STORAGE
Do not store above 30°C
Protect from light and moisture.

The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED
Onseget (Ondansetron) Tablets 8mg are available in pack of 10's.

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

Manufactured by:

Getz pharma (PVT) LIMITED
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