120 x 160mm

Emesson®

(Ondansetron)

Highnoon

COMPOSITION
Emesson 4mg Tablets: Each film-coated tablet contains:
Ondansetron HCl Dihydrate eq. to Ondansetron 4mg

Emesson 8mg Tablets: Each film-coated tablet contains:
Ondansetron HCl Dihydrate eq. to Ondansetron 8mg

Emesson Oral Solution: Each 5mL contains:
Ondansetron HCl Dihydrate eq. to Ondansetron 4mg

DESCRIPTION
Ondansetron is a potent, highly selective 5-HT3 receptor-antagonist.

MECHANISM OF ACTION
Its precise mode of action in the control of nausea and vomiting is not known. Chemotherapeutic agents and radiotherapy may cause release of 5-HT in the small intestine initiating a vomiting reflex by activating vagal afferents via 5-HT3 receptors. Ondansetron blocks the initiation of this reflex. Activation of vagal afferents may also cause a release of 5-HT 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 5-HT3 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. Ondansetron does not alter plasma prolactin concentrations. The role of ondansetron in opiate-induced emesis is not yet established.

PHARMACOKINETICS
Peak plasma concentration of ondansetron occurs about 1.5 hours after an oral dose of 8 mg and about 6 hours after a rectal dose. The absolute bioavailability is about 60% mainly because of hepatic first pass metabolism. In elderly subjects, bioavailability may be somewhat higher (65%) and clearance lower, presumably due to reduced hepatic first pass metabolism. Ondansetron is extensively distributed in the body, about 70% to 75% of the drug in plasma is protein bound. It is metabolized in the liver through multiple enzymatic pathways. Ondansetron is a substrate for cytochrome P450 isoenzyme, primarily CYP3A4, but also, CYP1A2 and CYP2D6. Less than 5% of dose is excreted unchanged in the urine. The terminal elimination half-life is about 3 hours after oral or parenteral doses, and about 6 hours after rectal use. The terminal elimination half-life is prolonged to about 5 hours in the elderly and those with renal impairment. These differences are not considered sufficient to warrant dosage adjustment. However, in patient with severe hepatic impairment, bioavailability may approach 100% and clearance is markedly reduced with elimination half-lives of 15 to 20 hours, dosage restriction is advisable. In general children have a higher clearance than adults, although age related reductions in clearance have also been reported in younger children having lower clearance. Use of weight-based doses compensate for these changes and normalize exposure in hepatic patients.

INDICATIONS AND USAGE
In adult it is indicated for the:
- Prevention and treatment of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy.
- Prevention and treatment of post-operative nausea and vomiting (PONV)

In Pediatric Population it is indicated for the:
- Management of chemotherapy-induced nausea and vomiting (CINV) in children aged ≥ 6 months.
- Prevention and treatment of PONV in children aged ≥1 month.

DOSAGE AND ADMINISTRATION
Adult Recommended Dosage Regimen for Prevention of Nausea and Vomiting
The dosage of ondansetron should be flexible in the range of 8-32 mg a day. The total daily dose must not exceed adult dose of 32 mg.

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/m^2 may be used.
Or for highly emetogenic chemotherapy a single dose of up to 24 mg ondansetron taken with 12 mg oral dexamethasone sodium phosphate, 1 to 2 hours before chemotherapy, can be used.

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.
To protect against delayed or prolonged emesis after the first 24 hours, oral or rectal treatment with ondansetron should be continued for up to 5 days after a course of treatment. The recommended dose for oral administration is 8 mg twice daily.

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.
Paediatric Recommended Dosage Regimen for Prevention of Nausea and Vomiting 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 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.
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.

BSA-based dosing for chemotherapy-Children aged ≥6 months and adolescents

Body surface area	Day1[a,b]	Days 2-6[b]
< 0.6m^2	5 mg/m^2 IV plus 2mg tablet after 12 hours	2 mg tablet every 12 hours
> 0.6m^2	5 mg/m^2 IV plus 4mg tablet after 12 hours	4 mg tablet every 12 hours
> 1.2m^2	5 mg/m^2 or 8mg IV plus 8mg tablet after 12 hours	8 mg tablet every 12 hours

Weight-based dosing for chemotherapy-children aged ≥6 months and adolescents

Weight	Day1[a,b]	Days 2-6[b]
≤ 10kg	Up to 3 doses of 0.15mg/kg at 4 - hourly intervals	2 mg tablet every 12 hours
> 10kg	Up to 3 doses of 0.15mg/kg at 4 - hourly intervals	4 mg tablet every 12 hours

a: The intravenous dose must not exceed 8mg. b: The total daily dose must not exceed adult dose of 32mg.

Post-operative nausea and vomiting (PONV)
Adults
For the prevention of PONV ondansetron can be administered orally. For oral administration: 16 mg one hour prior to anaesthesia. Alternatively, 8 mg one hour prior to anaesthesia followed by two further doses of 8 mg at eight hourly intervals. For the treatment of established PONV intravenous or intramuscular administration is recommended.
Elderly
Ondansetron is well tolerated in patients over 65 years receiving chemotherapy no alteration of dosage, dosing frequency or route of administration are required.

Patients with renal impairment
No alteration of daily dosage or frequency of dosing, or route of administration are required.

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 8 mg should not be exceeded.

Patients with poor sparteine/debrisoquine metabolism
The elimination half-life of ondansetron is not altered in subjects classified as poor metabolisers of sparteine and debrisoquine. Consequently in such patients, repeat dosing will give medicinal product exposure levels no different from those of the general population. No alteration of daily dosage or frequency of dosing is required.

CONTRAINDICATIONS
- Hypersensitivity to the active substance or to other selective 5-HT3 receptor antagonists (e.g., granisetron, dolasetron) or to any of the excipients
- Concomitant use with apomorphine
- Congenital long QT syndrome

WARNINGS AND PRECAUTIONS
- 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.
- Ondansetron prolongs the QT interval in a dose-dependent manner. Cases of Torsade de Pointes have been reported in patients using ondansetron. Avoid ondansetron in patients with congenital long QT syndrome. Ondansetron should be administered with caution to patients who have or may develop prolongation of QTc. These conditions include patients with electrolyte abnormalities, congestive heart failure, brady arrhythmias or patients taking other medicinal products that lead to QT prolongation or electrolyte abnormalities.
- Hypokalemia and hypomagnesaemia should be corrected prior to ondansetron administration.
- There have been reports describing patients with serotonin syndrome (including altered mental status, autonomic instability, and neuromuscular abnormalities) following the concomitant use of ondansetron and other serotonergic drugs (including selective serotonin reuptake inhibitors (SSRI) and serotonin noradrenaline reuptake inhibitors (SNRIs). If concomitant treatment with ondansetron and other serotonergic drugs is clinically warranted, appropriate observation of the patient is advised.
- 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 Aden tonsillar surgery prevention of nausea and vomiting with ondansetron may mask occult bleeding. Therefore, such patients should be followed carefully after ondansetron.
- The use of ondansetron in patients following abdominal surgery or in patients with chemotherapy-induced nausea and vomiting may mask a progressive ileus and gastric distention.
- Ondansetron Is not a drug that stimulates gastric or intestinal peristalsis. It should not be used instead of nasogastric suction.

Pediatric Population:
- Pediatric patients receiving ondansetron with hepatotoxic chemotherapeutic agents should be monitored closely for impaired hepatic function.
- CINV: When calculating the dose on an mg/kg basis and administering three doses at 4-hourly intervals, the total daily dose will be higher than if one single dose of 5mg/m² followed by an oral dose is given.

ADVERSE REACTIONS
The reported adverse events are: immediate hypersensitivity reactions including severe anaphylaxis (angioedema, bronchospasm, cardiopulmonary arrest, hypotension, laryngeal oedema, laryngospasm, shock, shortness of breath, stridor), headache, diarrhea, fever, cold sensation, pruritus, paresthesia, involuntary movement disorder such as extrapyramidal reactions e.g. oculogyric crisis / dystonic reactions, dyskinesia, seizures (e.g. epileptic spasm), dizziness, depression, transient visual disturbances (e.g. blurred vision, transitory blindness), drowsiness, constipation, hypokalemia, chest pain with or without ST segment depression, hypotension, cardiac arrhythmias (including ventricular and supraventricular tachycardia, premature ventricular contraction and atrial fibrillation), bradycardia, tachycardia, transitory changes in the electrocardiogram (including second degree heart block, ST segment depression), QTc prolongation (including Torsades de Pointes), palpitation, syncope, sensation of flushing or warmth, pain, redness and burning at site of injection, hiccups, rise in liver enzymes (aspartate transaminase and alanine transaminase), hypersensitivity reactions around the injection site (e.g. urticaria, rash, itching), Stevens-Johnson Syndrome and toxic epidermal necrolysis.

DRUG 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. It does not interact with alcohol, temazepam, furosemide, alfentanil, morphine, lignocaine, propofol and thiopental.

Effects of other medicinal products on ondansetron
- Ondansetron is metabolized by multiple hepatic cytochrome P-450 enzymes: CYP3A4, CYP2D6 and CYP1A2. Due to the multiplicity of metabolic enzymes capable of metabolizing 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. 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.
- There have been reports describing patients with serotonin syndrome (including altered mental status, autonomic instability, and neuromuscular abnormalities) following the concomitant use of ondansetron and other serotonergic drugs (including SSRIs and SNRIs).
- Based on reports of profound hypotension and loss of consciousness when ondansetron was administered with apomorphine hydrochloride, concomitant use with apomorphine is contraindicated.
- In patients treated with potent inducers of CYP3A4 (i.e. phenytoin, carbamazepine and rifampicin), the oral clearance of ondansetron was increased and ondansetron blood concentrations were decreased.
- Ondansetron may reduce the analgesic effect of tramadol.

USE IN SPECIFIC POPULATIONS
Pregnancy
Ondansetron has been reported to readily cross the placenta and significant amount has been found in all embryonic compartment. Ondansetron is suspected to cause orofacial malformations when administered during the first trimester of pregnancy. Its use during first trimester use was associated with an increased risk of oral clefts. Ondansetron should not be used during the first trimester of pregnancy.

Lactation
It is recommended that mothers receiving ondansetron should not breast-feed their babies.
Women of childbearing potential
Women of childbearing potential should consider the use of contraception.

Renal Impairment
No alteration of daily dosage or frequency of dosing, or route of administration is required.

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 8 mg should not be exceeded.

Poor sparteine/debrisoquine metabolism
The elimination half-life of ondansetron is not altered in subjects classified as poor metabolizers of sparteine and debrisoquine. Consequently, in such patients repeat dosing will give drug exposure levels no different from those of the general population. No alteration of daily dosage or frequency of dosing is required.

Effects on ability to drive and use machines
Ondansetron 2 mg/ml has no or negligible influence on the ability to drive and use machines.

OVERDOSAGE
The symptoms manifested with overdosage with ondansetron are visual disturbances, severe constipation, hypotension and a vasovagal episode with transient second-degree AV block. In all instances, the events resolved completely. Ondansetron prolongs the QT interval in a dose-dependent fashion. ECG monitoring is recommended incases of overdose. There is no specific antidote for ondansetron, therefore in all cases of suspected overdose, symptomatic and supportive therapy should be given as appropriate. 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.

DOSAGE & INSTRUCTIONS
To be sold and used on the prescription of a registered medical practitioner only. Keep out of reach of children. Do not store above 30ºC. Keep in a dry place. Protect from light.

PRESENTATION
Emesson 4mg Tablets:
Alu. Alu. Blister Pack of 1 x 10's.

Emesson 8mg Tablets:
Alu. Alu. Blister Pack of 1 x 10's.

Emesson Oral Solution:
Glass Amber bottle of 50mL

ایمیسن®

(اونڈنسیٹرون)

خوراک و ہدایات:

صرف مستند ڈاکٹر کے نسخہ کے مطابق ہی دوا فروخت اور استعمال کی جائے۔
بچوں کی پہنچ سے دور رکھیں۔ 30°C سے زیادہ درجہ حرارت پر نہ رکھیں۔
خشک جگہ پر رکھیں۔ روشنی سے بچائیں۔

Manufactured by:
HIGHNOON LABORATORIES LTD
17.5 KM, Multan Road, Lahore, Pakistan.
www.highnoon-labs.com

Item Code No. 14003710

120 x 160mm