140mm

210mm

Syrup/Injection/Tablet

DESTON

(Ondansetron HCl)

ڈیسٹن

ٹیبلٹ / انجیکشن / سیرپ

(اونڈینسٹرون ہائیڈروکلورائیڈ)

COMPOSITION:

DESTON Syrup 4mg/5ml

Each 5ml contains:

Ondansetron (as hydrochloride dihydrate).....4mg

(USP Specifications)

DESTON Injection 8mg/4ml

Each 4ml ampoule contains:

Ondansetron (as hydrochloride).....8mg

(USP Specifications)

DESTON Tablet 8mg

Each film coated tablet contains:

Ondansetron (as hydrochloride dihydrate).....8mg

(USP Specifications)

DESCRIPTION:

Ondansetron is used to prevent nausea and vomiting caused by cancer chemotherapy, radiation therapy, and surgery. Ondansetron is in a class of medications called serotonin 5-HT3 receptor antagonists. It works by blocking the action of serotonin, a natural substance that may cause nausea and vomiting.

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, peripherally, 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 serotonin may stimulate the vagal afferents through the 5-HT3 receptors and initiate the vomiting reflex.

INDICATIONS:

DESTON is indicated for the prevention of nausea and vomiting associated with:

- Highly emetogenic cancer chemotherapy, including cisplatin greater than or equal to 50mg/m^2
- 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.

DESTON is also indicated for the prevention of postoperative nausea and/or vomiting.

DOSAGE AND ADMINISTRATION:

Oral Dosage:

Adult Recommended Dosage Regimen for Prevention of Nausea and Vomiting

Indications	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 50mg/m^2
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 anaesthesia.

Paediatric Recommended Dosage Regimen for Prevention of Nausea and Vomiting

Indications	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.

Dosage in Hepatic Impairment:

In patients with severe hepatic impairment (Child-Pugh score of 10 or greater), do not exceed a total daily dose of 8 mg.

Injection Dosage:

Prevention of Nausea and Vomiting Associated with Initial and Repeat Courses of Emetogenic Chemotherapy

DESTON Injection should be diluted in 50 mL of 5% Dextrose Injection or 0.9% Sodium Chloride Injection before administration.

Adults:

The recommended adult intravenous dosage of DESTON is three 0.15-mg/kg doses up to a maximum of 16 mg per dose. The first dose is infused over 15 minutes beginning 30 minutes before the start of emetogenic chemotherapy.

Subsequent doses (0.15 mg/kg up to a maximum of 16 mg per dose) are administered 4 and 8 hours after the first dose of DESTON.

Pediatrics:

For pediatric patients 6 months through 18 years of age, the intravenous dosage of DESTON is three 0.15-mg/kg doses up to a maximum of 16 mg per dose.

The first dose is to be administered 30 minutes before the start of moderately to highly emetogenic chemotherapy.

Subsequent doses (0.15 mg/kg up to a maximum of 16 mg per dose) are administered 4 and 8 hours after the first dose of DESTON. The drug should be infused intravenously over 15 minutes.

Prevention of Postoperative Nausea and Vomiting

DESTON Injection should not be mixed with solutions for which physical and chemical compatibility have not been established. In particular, this applies to alkaline solutions as a precipitate may form.

Adults:

The recommended adult intravenous dosage of DESTON is 4 mg undiluted administered intravenously in not less than 30 seconds, preferably over 2 to 5 minutes, immediately before induction of anesthesia, or postoperatively if the patient did not receive prophylactic anti-emetics and experiences nausea and/or vomiting occurring within 2 hours after surgery. Alternatively, 4 mg undiluted may be administered intramuscularly as a single injection for adults. While recommended as a fixed dose for patients weighing more than 40 kg, few patients above 80 kg have been studied. In patients who do not achieve adequate control of postoperative nausea and vomiting following a single, prophylactic, pre induction, intravenous dose of ondansetron 4 mg, administration of a second intravenous dose of 4 mg ondansetron postoperatively does not provide additional control of nausea and vomiting.

Pediatrics:

For pediatric patients 1 month through 12 years of age, the dosage is a single 0.1-mg/kg dose for patients weighing 40 kg or less, or a single 4-mg dose for patients weighing more than 40 kg. The rate of administration should not be less than 30 seconds, preferably over 2 to 5 minutes immediately prior to or following anesthesia induction, or postoperatively if the patient did not receive prophylactic anti-emetics and experiences nausea and/or vomiting occurring shortly after surgery. Prevention of further nausea and vomiting was only studied in patients who had not received prophylactic DESTON.

Stability and Handling

After dilution, do not use beyond 24 hours. Although DESTON Injection is chemically and physically stable when diluted as recommended, sterile precautions should be observed because diluents generally do not contain preservative.

Dosage Adjustment for Patients with Impaired Hepatic Function

In patients with severe hepatic impairment (Child-Pugh score of 10 or greater), a single maximal daily dose of 8 mg infused over 15 minutes beginning 30 minutes before the start of the emetogenic chemotherapy is recommended. There is no experience beyond first-day administration of ondansetron in these patients.

PHARMACOKINETICS:

Absorption:

Ondansetron is absorbed from the gastrointestinal tract and undergoes some first-pass metabolism. Mean bioavailability in healthy subjects, following administration of a single 8-mg tablet, is approximately 56%. Ondansetron systemic exposure does not increase proportionately to dose. The AUC from a 16-mg tablet was 24% greater than predicted from an 8-mg tablet dose. This may reflect some reduction of first-pass metabolism at higher oral doses.

Food Effects: Bioavailability is also slightly enhanced by the presence of food.

Distribution:

Plasma protein binding of ondansetron as measured in vitro was 70% to 76% over the concentration range of 10 to 500 ng/mL. Circulating drug also distributes into erythrocytes.

Metabolism and Excretion:

Ondansetron is extensively metabolized in humans, with approximately 5% of a radiolabelled dose recovered as the parent compound from the urine. The metabolites are observed in the urine. The primary metabolic pathway is hydroxylation on the indole ring followed by subsequent glucuronide or sulfate conjugation. In vitro metabolism studies have shown that ondansetron is a substrate for human hepatic cytochrome P-450 enzymes, including CYP1A2, CYP2D6, and CYP3A4. In terms of

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overall ondansetron turnover, CYP3A4 played the predominant role. Because of the multiplicity of metabolic enzymes capable of metabolizing ondansetron, it is likely that inhibition or loss of one enzyme (e.g., CYP2D6 genetic deficiency) will be compensated by others and may result in little change in overall rates of ondansetron elimination. Although some non-conjugated metabolites have pharmacologic activity, these are not found in plasma at concentrations likely to significantly contribute to the biological activity of ondansetron.

WARNINGS AND PRECAUTIONS:

Hypersensitivity Reactions

Hypersensitivity reactions, including anaphylaxis and bronchospasm, have been reported in patients who have exhibited hypersensitivity to other selective 5-HT3 receptor antagonists. If hypersensitivity reactions occur, discontinue use of DESTON; treat promptly per standard of care and monitor until signs and symptoms resolve.

QT Prolongation

Electrocardiogram (ECG) changes including QT interval prolongation have been seen in patients receiving ondansetron. In addition, post marketing cases of Torsade de Pointes have been reported in patients using Ondansetron. Avoid DESTON in patients with congenital long QT syndrome. ECG monitoring is recommended in patients with electrolyte abnormalities (e.g., hypokalaemia or hypomagnesemia), congestive heart failure, bradyarrhythmias, or patients taking other medicinal products that lead to QT prolongation.

Serotonin Syndrome

The development of serotonin syndrome has been reported with 5-HT3 receptor antagonists alone. 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 DESTON alone has also been reported. The majority of reports of serotonin syndrome related to 5-HT3 receptor antagonist use occurred in a post-anesthesia care unit or an infusion center. Symptoms associated with serotonin syndrome may include the following combination of signs and symptoms: mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, and hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, and incoordination), and seizures, with or without gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Patients should be monitored for the emergence of serotonin syndrome, especially with concomitant use of DESTON and other serotonergic drugs. If symptoms of serotonin syndrome occur, discontinue DESTON and initiate supportive treatment. Patients should be informed of the increased risk of serotonin syndrome, especially if DESTON is used concomitantly with other serotonergic drugs.

Masking of Progressive Ileus and Gastric Distension

The use of DESTON 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. DESTON is not a drug that stimulates gastric or intestinal peristalsis. It should not be used instead of nasogastric suction.

Pregnancy

Pregnancy Category B

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Ondansetron is excreted in the breast milk of rats. It is not known whether ondansetron is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ondansetron is administered to a nursing woman.

ADVERSE REACTIONS:

Cardiovascular

Arrhythmias (including ventricular and supraventricular tachycardia, premature ventricular contractions, and atrial fibrillation), bradycardia, electrocardiographic alterations (including second-degree heart block, QT/QTc interval prolongation, and ST segment depression), palpitations, and syncope. Rarely and predominantly with intravenous ondansetron, transient ECG changes including QT interval prolongation have been reported.

General

Flushing. Rare cases of hypersensitivity reactions, sometimes severe (e.g., anaphylactic reactions, angioedema, bronchospasm, shortness of breath, hypotension, laryngeal edema, stridor) have also been reported. Laryngospasm, shock, and cardiopulmonary.
arrest have occurred during allergic reactions in patients receiving injectable ondansetron.

Hepatobiliary

Liver enzyme abnormalities.

Lower Respiratory

Hiccups.

Neurology

Oculogyric crisis, appearing alone, as well as with other dystonic reactions.

Skin

Urticaria, Stevens-Johnson syndrome, and toxic epidermal necrolysis.

Eye Disorders

Cases of transient blindness, predominantly during intravenous administration, have been reported. These cases of transient blindness were reported to resolve within a few minutes up to 48 hours.

DRUG INTERACTIONS:

Serotonergic Drugs

Serotonin syndrome (including altered mental status, autonomic instability, and neuromuscular symptoms) has been described following the concomitant use of 5-HT3 receptor antagonists and other serotonergic drugs, including selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs). Monitor for the emergence of serotonin syndrome. If symptoms occur, discontinue DESTON and initiate supportive treatment.

Drugs Affecting Cytochrome P-450 Enzymes

Ondansetron does not itself 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. 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. However, on the basis of available data, no dosage adjustment for DESTON is recommended for patients on these drugs.

Tramadol

Although no pharmacokinetic drug interaction between ondansetron and tramadol has been observed, data from 2 small trials indicate that when used together, DESTON may increase patient-controlled administration of tramadol. Monitor patients to ensure adequate pain control when ondansetron is administered with tramadol.

Apomorphine

Based on reports of profound hypotension and loss of consciousness when apomorphine was administered with ondansetron, the concomitant use of apomorphine with ondansetron is contraindicated

Chemotherapy

Carmustine, etoposide, and cisplatin do not affect the pharmacokinetics of ondansetron. In a crossover trial in 76 pediatric patients, intravenous ondansetron did not increase systemic concentrations of high-dose methotrexate.

Alfentanil and Atracurium

DESTON does not alter the respiratory depressant effects produced by alfentanil or the degree of neuromuscular blockade produced by atracurium. Interactions with general or local anesthetics have not been studied.

CONTRAINDICATIONS:

DESTON is contraindicated in patients:
Known to have hypersensitivity (e.g., anaphylaxis) to ondansetron or any of the components of the formulation.
Receiving concomitant apomorphine due to the risk of profound hypotension and loss of consciousness.

STORAGE & INSTRUCTIONS:

Storage temperature for **tablet & injection**: 2-30°C.
Storage temperature for **syrup**: 15-30°C.
Protect from heat, sunlight and moisture.
Keep away from the reach of children.
To be sold on prescription of registered medical practitioner only.

HOW SUPPLIED:

DESTON Syrup 4mg/5ml
50ml
DESTON Injection 8mg/4ml
4ml x 1's, 4ml x 5's ampoules
DESTON Tablet 8mg
10's tablets

خوراک وطریقہ استعمال:
ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

ہدایات:
ٹیبلٹ اور انجیکشن کو ۲-۳۰ اور سیرپ کو ۱۵-۳۰ ڈگری سینٹی گریڈ
درجہ حرارت کے درمیان رکھیں۔
دوا کو دھوپ، گرمی اور نمی سے بچائیں۔ بچوں کی پہنچ سے دور رکھیں۔
صرف مستند ڈاکٹر کے نسخے پر فروخت کریں۔

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