For the use of only a Registered Medical Practitioner or a Hospital or a Laboratory

Not to be sold by retail without the prescription of a Registered Medical Practitioner

Prescribing Information

1. Generic Name

Ondansetron Orally Disintegrating Tablets IP 4 mg
(Brand Name: ETERNA®-MD Tablets)

2. Qualitative and Quantitative Composition

Each uncoated orally disintegrating tablet contains:
Ondansetron IP …….. 4 mg.
Excipients …….. q.s.
Colour: Erythrosine Lake

3. Dosage Form and Strength

Dosage Form: Tablets.
Dosage Strength: Ondansetron 4 mg per tablet.

4. Clinical Particulars

4.1 Therapeutic Indication

ETERNA-MD Tablets are indicated in the following:

- Prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy.
- Prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy.
- Prevention of nausea and vomiting associated with radiotherapy.
- Prevention of postoperative nausea and vomiting.

4.2Posology and Method of Administration

Dosage in Adults

1. **Chemotherapy-Induced Nausea and Vomiting.**
   - **Highly Emetogenic Cancer Chemotherapy (HEC):** Recommended dose: 24 mg orally 30 minutes before the start of single-day HEC (including cisplatin doses of 50 mg/m^2 or greater). Multiday, single-dose administration of ondansetron 24 mg has not been studied.

   - **Moderately Emetogenic Cancer Chemotherapy (MEC):** Recommended dose: 8 mg orally twice a day, with the first dose administered 30 minutes before the start of chemotherapy and the subsequent dose 8 hours later; then 8 mg orally 2 times a day (every 12 hours) for 1 to 2 days after the completion of chemotherapy.

2. Radiation-Induced Nausea and Vomiting.

Usual recommended dose: 8 mg orally 3 times a day.

- **Total Body Irradiation:** 8 mg orally 1 to 2 hours before each fraction of radiotherapy administered each day.

- **Single High-dose Fraction Radiotherapy to the Abdomen:** 8 mg orally 1 to 2 hours before radiotherapy, with subsequent doses every 8 hours after the first dose for 1 to 2 days after the completion of radiotherapy.

- **Daily Fractionated Radiotherapy to the Abdomen:** 8 mg orally 1 to 2 hours before radiotherapy, with subsequent doses every 8 hours after the first dose for each day radiotherapy is given.

3. Postoperative Nausea and Vomiting.

Recommended dose: 16 mg orally 1 hour before the induction of anesthesia. Alternatively, 8 mg one hour prior to anesthesia followed by two further doses of 8 mg at eight hourly intervals.

In adults, the total daily dose of ondansetron for any indication should not exceed 32 mg.
Or, as prescribed by the physician.

<u>Paediatric Dosage</u>

1. Chemotherapy-Induced Nausea and Vomiting in Children ≥6 Months Old and Adolescents.

- **Based on Age Group**
  - Children Between 4 to 11 Years of Age: 4 mg 2 to 3 times daily.
  - Children 12 Years and Older: 8 mg twice a day.

- **Based on Body Weight**
  - < 10 kg: 0.15 mg/kg/dose or 2 mg every 12 hours.
  - > 10 kg: 0.15 mg/kg/dose or 4 mg every 12 hours.

- **Based on Body Surface Area**
  - < 0.6 m^2: 2 mg every 12 hours.
  - > 0.6 m^2: 4 to 8 mg every 12 hours.

The total daily dose of ondansetron in paediatric patients must not exceed the adult dose of 32 mg.

2. Radiotherapy-Induced Nausea and Vomiting in Children.

Safety and effectiveness of ondansetron in paediatric patients have not been established for this indication.

3. Post-Operative Nausea and Vomiting in Children ≥1 Month Old and Adolescents.

No studies have been conducted on the use of orally administered ondansetron in the prevention or treatment of post-operative nausea and vomiting; slow intravenous injection (not less than 30 seconds) is recommended for this purpose.

Or, as prescribed by the physician.

Directions for Administration of Orally Disintegrating Tablet

Remove tablet from packaging just prior to dosing. Immediately place the ETERNA-MD Tablet on top of the tongue where it will disintegrate in seconds, then swallow with saliva or liquid. Tablets may be administered with or without water.

4.3Contraindications

ETERNA-MD Tablets are contraindicated in the following:

- Known hypersensitivity (e.g., anaphylaxis) to ondansetron or to any component of the formulation.
- Concomitant apomorphine therapy due to the risk of profound hypotension and loss of consciousness.

4.4Special Warnings and Precautions for Use

Hypersensitivity Reactions: Hypersensitivity reactions, including anaphylaxis and bronchospasm, have been reported in patients who have exhibited hypersensitivity to other selective $5HT_3$ (5-hydroxy triptamine) receptor antagonists. If hypersensitivity reactions occur, discontinue use of ondansetron and treat promptly and appropriately.

QT Prolongation: Electrocardiogram (ECG) changes including QT interval prolongation have been observed in patients receiving ondansetron. 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. 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.

Serotonin Syndrome: The development of serotonin syndrome has been reported with $5HT_3$ receptor antagonists alone. Most reports have been associated with concomitant use of serotonergic drugs (e.g., selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, monoamine oxidase inhibitors, mirtazapine, fentanyl, lithium, and tramadol).

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, hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), 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 ondansetron and other serotonergic drugs. If

symptoms of serotonin syndrome occur, discontinue ondansetron and initiate supportive treatment. Patients should be informed of the increased risk of serotonin syndrome, especially if ondansetron is used concomitantly with other serotonergic drugs.

Masking of Progressive Ileus and Gastric Distension: 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. Ondansetron does not stimulate gastric or intestinal peristalsis. It should not be used instead of nasogastric suction.

4.5Drug Interactions

Serotonergic Drugs: Serotonin syndrome (including altered mental status, autonomic instability, and neuromuscular symptoms) has been reported following the concomitant use of $5HT_3$ 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 ondansetron and initiate supportive treatment.

Cytochrome P450 Enzymes Inducers/Inhibitors: Ondansetron does not itself appear to induce or inhibit the cytochrome P450 drug-metabolizing enzyme system of the liver. Because ondansetron is metabolized by hepatic cytochrome P450 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 ondansetron 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, ondansetron may increase patient-controlled administration of tramadol. It is recommended to monitor patients when ondansetron is administered with tramadol.

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

4.6Use in Special Populations

Pregnant Women

Pregnancy Category B. Reproduction studies have been performed in pregnant rats and rabbits at daily oral doses up to 15 and 30 mg/kg/day, respectively, and have revealed no evidence of impaired fertility or harm to the fetus due to ondansetron. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, ondansetron therapy should be used during pregnancy only if clearly needed.

Lactating Women

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.

Paediatric Patients

The safety and effectiveness of orally administered ondansetron have not been established in paediatric patients below 6 months of age for the prevention of nausea and vomiting associated with cancer chemotherapy. For paediatric usage, please refer 'Posology and Method of Administration' section.

Geriatric Patients

No overall differences in safety or effectiveness were observed between elderly (> 65 years) and younger subjects. A reduction in clearance and increase in elimination half-life have been seen in patients older than 75 years compared with younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Usually, no dosage adjustment is required in the geriatric population.

Renal Impairment Patients

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. Dosage adjustment is usually not required for patients with any degree of renal impairment (mild, moderate, or severe).

Hepatic Impairment Patients

No dosage adjustment is needed in patients with mild or moderate hepatic impairment. In patients with severe hepatic impairment, clearance is reduced by 2 to 3-fold and apparent volume of distribution is increased with a resultant increase in half-life to 20 hours. Therefore, a total daily dose of 8 mg should not be exceeded in patients with severe hepatic impairment.

4.7Effect on Ability to Drive and Use Machines

Ondansetron has no or negligible influence on the ability to drive and use machines.

4.8Undesirable Effects

Clinical Trials Experience

The most commonly reported adverse reactions with ondansetron in controlled clinical trials include the following: Headache, malaise, fatigue, constipation, diarrhea, pyrexia, dizziness, pruritus, gynecological disorders, anxiety/agitation, urinary retention etc.

Other less commonly adverse reactions include:

Central Nervous System: Extrapyramidal reactions.

Hepatic: Elevations in aspartate transaminase (AST) and/or alanine transaminase (ALT) values.
Others: Rash, anaphylaxis, bronchospasm, tachycardia, angina, hypokalemia, electrocardiographic alterations, vascular occlusive events, and grand mal seizures.

Post-Marketing Experience
The following adverse reactions have been identified during post-approval use of ondansetron. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
Cardiovascular: Arrhythmias (including ventricular and supraventricular tachycardia, premature ventricular contractions, and atrial fibrillation), bradycardia, transient electrocardiographic alterations (including second-degree heart block, QT/QTc interval prolongation, and ST segment depression), palpitations, and syncope.
General: Hiccups, flushing.
Hypersensitivity: Rare cases of hypersensitivity reactions such as anaphylactic reactions, angioedema, bronchospasm, shortness of breath, hypotension, laryngeal edema, and stridor have been reported.
Hepatobiliary: Liver enzyme abnormalities.
Neurological: Oculogyric crisis, appearing alone, as well as with other dystonic reactions.
Dermatological: Urticaria, Stevens-Johnson syndrome, and toxic epidermal necrolysis.

4.9Overdose
There is limited experience of ondansetron overdose. In the majority of cases, symptoms were similar to adverse/side effects reported in patients receiving recommended doses of ondansetron. Manifestations that have been reported include visual disturbances, severe constipation, hypotension, faintness, and a vasovagal episode with transient second-degree AV block. Ondansetron prolongs the QT interval in a dose-dependent manner.
There is no specific antidote for ondansetron overdose. Patients should be managed with appropriate supportive therapy. ECG monitoring is recommended in cases of overdose.
Overdose Experience in Paediatric Patients: Paediatric cases consistent with serotonin syndrome have been reported after inadvertent oral overdoses of ondansetron (exceeding estimated ingestion of 5 mg/kg) in young children. Reported symptoms included somnolence, agitation, tachycardia, tachypnea, hypertension, flushing, mydriasis, diaphoresis, myoclonic movements, nystagmus, hyperreflexia, and seizures. Patients required supportive care, including intubation in some cases, with complete recovery without sequelae within 1 to 2 days.

5. Pharmacological Properties
5.1 Mechanism of Action
Ondansetron is a potent, highly selective $5HT_3$ receptor antagonist. Serotonin receptors of the $5HT_3$ type are present both peripherally on vagal nerve terminals and centrally in the chemoreceptor trigger zone (CTZ) of the area postrema.

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 (peripheral mechanism). 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. Ondansetron blocks the initiation vomiting reflex. The effect of ondansetron in the management of the nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy is 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 chemotherapy-induced nausea and vomiting.
Ondansetron does not alter plasma prolactin concentrations.

5.2Pharmacodynamic Properties

Ondansetron is an antiemetic agent. The serotonin stimulates the vagal and splanchnic nerve receptors that project to the medullary vomiting center, as well as the 5-HT_3 receptors in the area postrema, thus initiating the vomiting reflex, causing nausea and vomiting.
Ondansetron is a highly specific and selective serotonin 5-HT_3 receptor antagonist, not shown to have activity at other known serotonin receptors and with low affinity for dopamine receptors. Ondansetron is useful for the treatment of nausea and vomiting due to cancer chemotherapy and also used to prevent and treat nausea and vomiting after surgery.

5.3Pharmacokinetic Properties

Absorption: Ondansetron is absorbed from the gastrointestinal tract and undergoes some first-pass metabolism. Mean bioavailability in healthy male subjects, following the oral administration of a single 8 mg tablet, is approximately 55 to 60%. Peak plasma concentration (26.2 to 42.7 ng/ml) is achieved in 1.7 to 2 hours. Ondansetron systemic exposure does not increase proportionately to dose. The area under curve (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. Bioavailability of ondansetron 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. Steady state volume of distribution is 140 liters. Circulating drug also distributes into erythrocytes.
Metabolism: Ondansetron is extensively metabolized in humans. The primary metabolic pathway is hydroxylation followed by subsequent glucuronide or sulfate conjugation. *In vitro* metabolism studies have shown that ondansetron is a substrate for human hepatic cytochrome P450 enzymes (CYP1A2, CYP2D6, and CYP3A4), mainly CYP3A4. 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 efficacy of ondansetron.

Excretion: Less than 5% of the absorbed dose is excreted unchanged in the urine. The metabolites are observed in the urine. Elimination half-life of ondansetron is about 3 hours.

6. Nonclinical Properties

6.1 Animal Toxicology

Carcinogenesis: Carcinogenic effects were not seen in 2-year studies in rats and mice with oral ondansetron doses up to 10 mg/kg per day and 30 mg/kg per day, respectively (approximately 4 and 6 times the maximum recommended human oral dose of 24 mg per day, based on body surface area).

Mutagenesis: Ondansetron was not mutagenic in standard tests for mutagenicity.

Impairment of Fertility: Oral administration of ondansetron up to 15 mg/kg per day (approximately 6 times the maximum recommended human oral dose of 24 mg per day, based on body surface area) did not affect fertility or general reproductive performance of male and female rats.

Developmental Toxicity: In embryo-fetal development studies in rats and rabbits, pregnant animals received oral doses of ondansetron up to 15 mg/kg/day and 30 mg/kg/day, respectively, during the period of organogenesis. With the exception of a slight decrease in maternal body weight gain in the rabbits, there were no significant effects of ondansetron on the maternal animals or the development of the offspring. At doses of 15 mg/kg/day in rats and 30 mg/kg/day in rabbits, the maternal exposure margin was approximately 6 and 24 times the maximum recommended human oral dose of 24 mg/day, respectively, based on body surface area.

In a pre-and postnatal developmental toxicity study, pregnant rats received oral doses of ondansetron up to 15 mg/kg/day from day 17 of pregnancy to litter day 21. With the exception of a slight reduction in maternal body weight gain, there were no effects upon the pregnant rats and the pre-and postnatal development of their offspring, including reproductive performance of the mated F1 generation. At a dose of 15 mg/kg/day in rats, the maternal exposure margin was approximately 6 times the maximum recommended human oral dose of 24 mg/day, based on body surface area.

7. Description

ETERNA-MD Tablets are Light Pink coloured, circular, flat faced beveled edged, orally disintegrating uncoated tablets with breakline on one side & plain on other side.

Each tablet of ETERNA-MD contains 4 mg of ondansetron for oral administration.

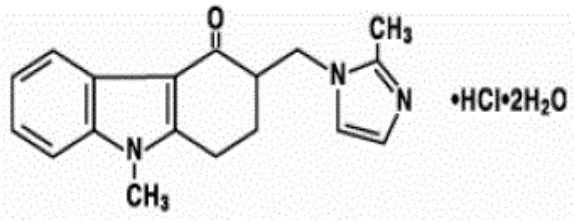
Ondansetron by selectively blocking serotonin 5-HT_3 receptor type produces antiemetic effect. Ondansetron hydrochloride dihydrate is a white to off-white powder that is soluble in water and normal saline.

Molecular Weight: 365.9 g/mol.

Chemical Name: (±) 1, 2, 3, 9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one, monohydrochloride, dihydrate.

Molecular Formula: $C_{18}H_{19}N_3O \cdot HCl \cdot 2H_2O$.

Structural Formula:



Inactive ingredients (excipients) of ETERNA-MD Tablets contains: Flavour Capsaroma peppermint, Colour Erythrosine Lake, Microcrystalline Cellulose, Colloidal Silicon Dioxide, Mannitol, Sucralose, Polyplasdone XL-10 & Magnesium Stearate.

8. Pharmaceutical Particulars

8.1 Incompatibilities

None known.

8.2Shelf-life

24 Months

8.3Packaging Information

Alu. Blister of 10 Tablets

8.4Storage and Handling Instructions

Store protected from light and moisture at a temperature not exceeding 30°C.
Keep out of reach of children.

9. Patient Counseling Information

Instructions to Patients

- Instruct patients to use this medicine exactly as prescribed and advised by your physician. Do not change the dose or stop this medicine without consulting your physician.
- Remove tablet from packaging just prior to dosing. Immediately place the ETERNA-MD Tablet on top of the tongue where it will disperse/dissolves within seconds, then swallow with saliva or liquid.
- Pregnant women and breastfeeding mother can use this medicine only if clearly needed and in consultation with their physician.
- This medicine is not recommended for use in children below 6 months old.
- Instruct patients to immediately consult their doctor if they perceive a change in their heart rate or if they feel lightheaded (this is because ondansetron may cause serious cardiac arrhythmias such as QT prolongation).
- Instruct patients to immediately report any signs or symptoms consistent with a potential bowel obstruction to their physician (this is because ondansetron may mask

signs and symptoms of bowel obstruction following abdominal surgery or those with chemotherapy-induced nausea and vomiting).

10. Details of Manufacturer

Pure & Cure Healthcare Pvt. Ltd.
(A Subsidary of Akums Drugs & Pharmaceuticals Ltd) Plot No. 26A, 27-30, Sector-8A, I.I.E., SIDCUL, Ranipur, Haridwar – 249403, Uttarakhand, INDIA.

11. Details of Permission or License Number with Date

Mfg. Lic. No. 31/UA/2013, Date of FDA Product Permission: 07/11/2014

12. Date of Revision

April 2021.

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EXCEL BLUE CROSS || EXCEL
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