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

# Prescribing Information

## 1. Generic Name

Ondansetron Injection IP

**(Brand Name: ETERNA® Injection)**

## 2. Qualitative and Quantitative Composition

**ETERNA Injection (2 ml ampoule)**

Each ml contains:

Ondansetron Hydrochloride IP eq. to Ondansetron ……..….. 2 mg

Water for Injection IP ……..…..… q.s.

**ETERNA Injection (10 ml multi-dose vial)**

Each ml contains:

Ondansetron Hydrochloride IP eq. to Ondansetron ……. 2 mg

Methylparaben IP (as preservative) …….. 1.2 mg

Propylparaben IP (as preservative) ……..….... 0.15 mg

Water for Injection IP …… q.s.

## 3. Dosage Form and Strength

Dosage Form: Injection.

Dosage Strength: Ondansetron 2 mg per ml.

## 4. Clinical Particulars

## 4.1 Therapeutic Indication

ETERNA injection is indicated in the following:

- Prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy and radiotherapy in adults and children aged above 6 months.
- Prevention and treatment of postoperative nausea and/or vomiting (PONV) in adults and children aged ≥1 month.

## 4.2Posology and Method of Administration

1. **Prevention of nausea and vomiting associated with initial and repeat courses of emetogenic chemotherapy:**

ETERNA Injection should be diluted in 50 ml of compatible diluents (5% Dextrose Injection or 0.9% Sodium Chloride Injection) before administration.

**Adults and pediatric patients aged above 6 months:** The recommended intravenous (I.V.) dosage is three doses of 0.15 mg/kg body weight 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. The drug should be infused intravenously over 15 minutes.

**2. Prevention of postoperative nausea and vomiting.**

**Adults:** The recommended dosage is 4 mg of ondansetron (undiluted) to be administered I.V. in not less than 30 seconds, preferably over 2 to 5 minutes. Ondansetron to be administered immediately before induction of anesthesia, or postoperatively if the patient did not receive prophylactic antiemetics and experiences nausea and/or vomiting within 2 hours after surgery.
Alternatively, 4 mg undiluted may be administered intramuscularly (I.M.) as a single injection.
**Pediatric patients 1 month to 12 years of age:** The recommended 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. Ondansetron to be administered immediately prior to or following anesthesia induction, or postoperatively if the patient did not receive prophylactic antiemetics and experiences nausea and/or vomiting shortly after surgery.
Or, as prescribed by the Physician.

**Compatible Diluents**

Following I.V. fluids are compatible for dilution:

- 0.9% Sodium Chloride Injection.
- 5% Dextrose Injection.
- 5% Dextrose and 0.9% / 0.45% Sodium Chloride Injection.
- 3% Sodium Chloride Injection.

**Pharmaceutical Precautions**

Each ampoule is for single use only. Solution should be used immediately after opening the ampoule. The unused portion, if any, should be discarded. Diluted solution (for I.V. infusion use), should be used within 24 hours. The infusion solution should not be used if crystals or precipitates are observed.
Vial is used for multiple (up to 5) doses/withdrawals. If a multi-dose vial has been opened or accessed (e.g., needle-punctured) the vial should be dated and used within 28 days. Strict aseptic technique should be used while removing a dose from vial; discard whenever sterility is compromised or questionable.
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if solution is not clear or has suspended matter.

## 4.3Contraindications

ETERNA Injection is contraindicated in patients known to have hypersensitivity (e.g., anaphylaxis) to ondansetron or to any component of this formulation.

The concomitant use of apomorphine with ondansetron is contraindicated as it may cause profound hypotension and loss of consciousness.

## 4.4Special Warnings and Precautions for Use

**Test Dose:** Before therapy with ETERNA Injection is instituted, a test dose is recommended to ascertain possibility of hypersensitivity to ingredients of ETERNA Injection. Serious acute hypersensitivity reactions may require the use of subcutaneous epinephrine and other emergency measures.

**Hypersensitivity Reactions:** Hypersensitivity reactions, including anaphylaxis and bronchospasm, have been reported in patients who have exhibited hypersensitivity to other selective 5-hydroxytryptamine (5-$HT_3$) receptor antagonists.

**QT Prolongation:** 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. 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 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 (MAO) inhibitors, mirtazapine, fentanyl, lithium, tramadol, and I.V. 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. 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 gastric distention.

**Effect on Peristalsis:** Ondansetron is not a drug that stimulates gastric or intestinal peristalsis. It should not be used instead of nasogastric suction.

## 4.5Drug Interactions

**Drugs Affecting Cytochrome P-450 Enzymes:** Ondansetron does not induce or inhibit the cytochrome P-450 (CYP) drug-metabolizing enzyme system of the liver. There is no evidence that ondansetron either induces or inhibits the metabolism of other drugs commonly co-administered with it and usually metabolized by CYP enzymes. Specific studies have shown that there are no interactions when ondansetron is administered with alcohol, temazepam, furosemide, morphine, lidocaine, thiopental, or propofol.

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.

**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.

**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. However, on the basis of available data, no dosage adjustment for ondansetron is recommended for patients on these drugs.

**Tramadol:** Although there are no data on pharmacokinetic drug interactions between ondansetron and tramadol, data from two small studies indicate that concomitant use of ondansetron may result in reduced analgesic activity of tramadol.

**Chemotherapy:** In humans, carmustine, etoposide, and cisplatin do not affect the pharmacokinetics of ondansetron. In a crossover study in 76 pediatric patients, I.V. ondansetron did not increase blood levels of high-dose methotrexate.

**Alfentanil and Atracurium:** Ondansetron 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.

**Drug Abuse and Dependence:** Animal studies have shown that ondansetron is not discriminated as a benzodiazepine nor does it substitute for benzodiazepines in direct addiction studies.

## 4.6Use in Special Populations

**Pregnant Women**

Pregnancy Category B. Reproduction studies have been performed in pregnant rats and rabbits at I.V. doses up to 4 mg/kg per day 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, this drug 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.

**Pediatric Patients**

Little information is available about the use of ondansetron in pediatric surgical patients younger than 1 month of age. Little information is available about the use of ondansetron in pediatric cancer patients younger than 6 months of age. The clearance of ondansetron in pediatric patients 1 month to 4 months of age is slower and the half-life is ~2.5 fold longer than patients who are 4 to 24 months of age. As a precaution, it is recommended that patients less than 4 months of age receiving this drug be closely monitored.

**Geriatric Patients**

No overall differences in safety or effectiveness were observed between elderly and younger patients. But, greater sensitivity of some older individuals cannot be ruled out. Dosage adjustment is generally not needed in patients over the age of 65 years.

**Hepatic Impairment Patients**

In patients with severe hepatic impairment, clearance is reduced and apparent volume of distribution is increased with a resultant increase in plasma half-life. In such patients, a total daily dose of 8 mg should not be exceeded.

**Renal Impairment Patients**

Although plasma clearance is reduced in patients with severe renal impairment (creatinine clearance < 30 ml/min), no dosage adjustment is recommended.

## 4.7Effect on Ability to Drive and Use Machines

In psychomotor testing ondansetron does not impair performance nor cause sedation. No detrimental effects on such activities are predicted from the pharmacology of ondansetron. ETERNA Injection has no or negligible influence on the ability to drive and use machines.

## 4.8Undesirable Effects

**Clinical Trials Experience**

Adverse reactions reported in ≥2% of patients were: Headache, drowsiness, injection site reaction, fever, cold sensation, pruritus, diarrhoea, and paresthesia.

Also, rash, constipation, elevated liver enzyme levels, extrapyramidal reactions, grand mal seizure, and hypokalemia were reported with use of ondansetron injection.

**Cardiovascular:** Rare cases of angina (chest pain), electrocardiographic alterations, hypotension, and tachycardia have been reported.

**Post-marketing Experience**

The following adverse reactions have been identified during post-approval use of ondansetron.

**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 I.V. ondansetron, transient ECG changes including QT/QTc interval prolongation have been reported.

**General:** Flushing. Rare cases of hypersensitivity reactions, sometimes severe (e.g., anaphylactic reactions, angioedema, bronchospasm, cardiopulmonary arrest, hypotension, laryngeal edema, laryngospasm, shock, shortness of breath, stridor) have also been reported. A positive lymphocyte transformation test to ondansetron has been reported, which suggests immunologic sensitivity to ondansetron.

**Hepatobiliary:** Liver enzyme abnormalities have been reported. Liver failure and death have been reported in patients with cancer receiving concurrent medications including potentially hepatotoxic cytotoxic chemotherapy and antibiotics.

**Local Reactions:** Pain, redness, and burning at site of injection.

**Lower Respiratory:** Hiccups.

**Neurological:** Oculogyric crisis, appearing alone, as well as with other dystonic reactions. Transient dizziness during or shortly after I.V. infusion.

**Skin:** Urticaria, Stevens-Johnson syndrome, and toxic epidermal necrolysis.

**Eye Disorders:** Cases of transient blindness, predominantly during I.V. administration, have been reported. These cases of transient blindness were reported to resolve within a few minutes up to 48 hours. Transient blurred vision, in some cases associated with abnormalities of accommodation, has also been reported.

## 4.9Overdose

There is no specific antidote for ondansetron overdose. Patients should be managed with appropriate supportive therapy. Individual I.V. doses as large as 150 mg and total daily I.V. doses as large as 252 mg have been inadvertently administered without significant adverse events. These doses are more than 10 times the recommended daily dose.

# 5. Pharmacological Properties

## 5.1 Mechanism of Action

Ondansetron is a potent, highly selective $5HT_3$ receptor-antagonist. 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 is due to antagonism of $5HT_3$ receptors on neurons located both in the peripheral and central nervous system.

## 5.2Pharmacodynamic Properties

Ondansetron is an antiemetic agent. Ondansetron is effectively used in the treatment of post-operative nausea and vomiting and cytotoxic drug-induced nausea and vomiting. Ondansetron selectively inhibits serotonin receptors i.e., $5HT_3$ receptors, present on neuronal cell surface. Ondansetron has no effect on esophageal motility, gastric motility, lower esophageal sphincter pressure, or small intestinal transit time.

## 5.3Pharmacokinetic Properties

The pharmacokinetic properties of ondansetron are unchanged on repeat dosing. A direct correlation of plasma concentration and anti-emetic effect has not been established.

**Absorption:** A 4 mg I.V. infusion of ondansetron given over 5 minutes results in peak plasma concentrations of about 65 ng/ml. Following I.M. 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, I.M. and I.V. dosing is similar with a steady state volume of distribution of about 140 l. Equivalent systemic exposure is achieved after I.M. and I.V. administration of ondansetron. Plasma protein binding of ondansetron is 70 to 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 polymorphism) 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.

# 6. Nonclinical Properties

## 6.1 Animal Toxicology

Carcinogenic effects were not seen in 2-year studies in rats and mice with oral ondansetron doses up to 10 and 30 mg/kg per day, respectively (approximately 3.6 and 5.4 times the recommended human I.V. dose of 0.15 mg/kg given three times a day, based on body surface area). Ondansetron was not mutagenic in standard tests for mutagenicity.

Oral administration of ondansetron up to 15 mg/kg per day (approximately 3.8 times the recommended human I.V. dose, based on body surface area) did not affect fertility or general reproductive performance of male and female rats.

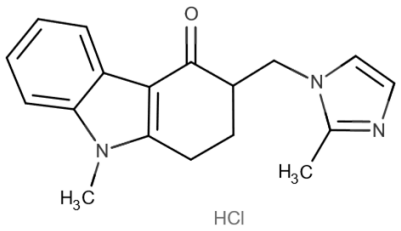
Reproduction studies have been performed in pregnant rats and rabbits at I.V. doses up to 4 mg/kg per day (approximately 1.4 and 2.9 times the recommended human I.V. dose of 0.15 mg/kg given three times a day, respectively, based on body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to ondansetron.

# 7. Description

ETERN Injection (2 ml ampoule) is clear, colourless solution filled in 2 ml clear glass ampoules with snap off red ring.

ETERN Injection (10 ml multi-dose vial) is clear, colourless solution filled in 10 ml amber glass vials.
Each ml of ETERNA Injection contains 2 mg of ondansetron for I.M. or I.V. use.

Ondansetron hydrochloride is a selective serotonin 5-$HT_3$ receptor blocker. Ondansetron hydrochloride is a white to off-white powder that is soluble in water and normal saline.
Molecular Weight: 329.8 g/mol.
Molecular Formula: C18H20ClN3O.
Chemical Name: 9-methyl-3-[(2-methylimidazol-1-yl)methyl]-2,3-dihydro-1H-carbazol-4-one; hydrochloride
Structural Formula:




Inactive ingredients (excipients) of ETERNA Injection (2 ml ampoule) contain Citric Acid, Sodium Chloride, and Tri – Sodium Citrate.
Inactive ingredients (excipients) of ETERNA Injection (10 ml multi-dose vial) contain Citric Acid, Methyl Paraben, Propyl Paraben, Sodium Chloride, and Tri – Sodium Citrate.

## 8. Pharmaceutical Particulars

### 8.1 Incompatibilities

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

### 8.2Shelf-life

Ampoule: 24 months.
Unopened multi-dose vial: 24 months.
Opened multi-dose vial: Punctured/opened vial should be used within 28 days after opening or when the expiry date is reached, whichever is sooner.

### 8.3Packaging Information

Ampoule: 2 ml glass ampoule for single dose.
Vial: 10 ml glass vial for multiple (up to 5) doses.

## 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

**Administration Instructions**

- Instruct patient to use medicine as advised and not to exceed the recommended dose.
- Advise patients to stop medicine and contact their healthcare provider as soon as possible if they develop any type of rash or if hypersensitivity/allergic reaction (e.g., difficulty breathing, swelling of the face, etc.) occur.
- Inform parents and caregivers not to use ETERNA Injection in infants less than 6 months of age for chemotherapy-induced nausea and vomiting and also not to use in infants below 1 month of age for post-operative nausea and vomiting.
- Instruct patients to use ampoule for single use only. Solution should be used immediately after opening and unused portion, if any, should be discarded. Diluted solution (for I.V. infusion use), should be used within 24 hours.
- Punctured/opened multi-dose vial of ETERNA Injection should be used within 28 days after opening. Discard unused portion, if any, and also not to use the injection whenever sterility is compromised or questionable (i.e., presence of cloudy precipitate).

## 10.Details of Manufacturer

Nitin Lifesciences Ltd.,
Rampur Road, Paonta Sahib, Dist Sirmour,
Himachal Pradesh – 173 025, India.

## 11. Details of Permission or License Number with Date

DCG(I) approval date: 12/02/1994.
**Ampoule:** Manufacturing license No. MB/05/209 dated 21/10/2005.
**Multi-dose vial:** Manufacturing license No. MB/05/209 dated 08/12/2008.

## 12. Date of Revision

January 2021.

Marketed by:

**EXCEL** BLUE CROSS || EXCEL

Division of

**BLUE CROSS LABORATORIES PVT LTD.**

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