

PRODUCT MONOGRAPH

PrTEVA-ONDANSETRON

Ondansetron Tablets, USP

4 mg and 8 mg ondansetron (as ondansetron hydrochloride dihydrate)

PrONDANSETRON INJECTION

Ondansetron Injection, USP

2 mg/mL ondansetron (as ondansetron hydrochloride dihydrate)

Antiemetic

(5-HT₃ receptor antagonist)

Teva Canada Limited
30 Novopharm Court
Toronto, Ontario
Canada M1B 2K9
www.tevacanada.com

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PrTEVA-ONDANSETRON
PrONDANSETRON INJECTION
(ondansetron hydrochloride dihydrate)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral	Tablets / 4 mg and 8 mg ondansetron (as ondansetron hydrochloride dihydrate)	Lactose monohydrate, magnesium stearate, microcrystalline cellulose, pregelatinized starch, sodium starch glycolate film-coating containing: hypromellose, hydroxypropyl methylcellulose, iron oxide yellow, macrogol, polyethylene glycol, polysorbate and titanium dioxide
Intravenous	Injection / 2 mg/mL ondansetron (as hydrochloride dihydrate)	2 mL and 4 mL vial: citric acid monohydrate, sodium chloride, sodium citrate dihydrate and water for injection. 20 mL vial: citric acid monohydrate, methylparaben, propylparaben, sodium chloride, sodium citrate dihydrate, and water for injection.

INDICATIONS AND CLINICAL USE

Adults

TEVA-ONDANSETRON and ONDANSETRON INJECTION (ondansetron hydrochloride) is indicated for:

- the prevention of nausea and vomiting associated with emetogenic chemotherapy, including high dose cisplatin, and radiotherapy,
- the prevention and treatment of post-operative nausea and vomiting.

Pediatrics (4-18 years of age)

Post-Chemotherapy Induced Nausea and Vomiting

Ondansetron hydrochloride was effective and well tolerated when given to children 4-12 years of age (see **DOSAGE AND ADMINISTRATION**). TEVA-ONDANSETRON and ONDANSETRON INJECTION are not indicated for the treatment of children 3 years of age or younger.

Post-Radiotherapy Induced Nausea and Vomiting

TEVA-ONDANSETRON and ONDANSETRON INJECTION are not indicated for use in any age group of this population.

Post-Operative Nausea and Vomiting

TEVA-ONDANSETRON and ONDANSETRON INJECTION are not indicated for use in any age group of this population.

Geriatrics (>65 years of age)

Post-Chemotherapy and Radiotherapy Induced Nausea and Vomiting

Efficacy and tolerance of ondansetron hydrochloride were similar to that observed in younger adults (see **DOSAGE AND ADMINISTRATION**).

Post-Operative Nausea and Vomiting

Clinical experience in the use of ondansetron hydrochloride in the prevention and treatment of post-operative nausea and vomiting is limited and is not indicated for use in this population.

CONTRAINDICATIONS

- TEVA-ONDANSETRON and ONDANSETRON INJECTION (ondansetron hydrochloride) are contraindicated in patients with a history of hypersensitivity to the drug or any components of its formulations. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the product monograph.
- 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.

WARNINGS AND PRECAUTIONS

Immune

Cross-reactive hypersensitivity has been reported between different 5-HT₃ antagonists. Patients who have experienced hypersensitivity reactions to one 5-HT₃ antagonist have experienced more severe reactions upon being challenged with another drug of the same class. The use of a different 5-HT₃ receptor antagonist is not recommended as a replacement in cases in which a patient has experienced even a mild hypersensitivity type reaction to another 5-HT₃ antagonist.

Cardiovascular

QTc Interval Prolongation: Ondansetron prolongs the QT interval (see **ACTION AND CLINICAL PHARMACOLOGY**, Electrocardiography). The magnitude of QTc prolongation will depend on the dose and the infusion rate. In addition, post-marketing cases of Torsade de Pointes have been reported in patients using ondansetron. Torsade de Pointes is a polymorphic ventricular tachyarrhythmia. Generally, the risk of torsade de pointes increases with the magnitude of QTc prolongation produced by the drug. Torsade de Pointes may be asymptomatic or experienced by the patient as dizziness, palpitations, syncope, or seizures. If sustained, torsade de pointes can progress to ventricular fibrillation and sudden cardiac death.

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, including congestive heart failure, bradyarrhythmias or patients taking other medicinal products that lead to either QT prolongation or electrolyte abnormalities (see **DRUG INTERACTIONS**). Hypokalemia, hypocalcemia, and hypomagnesemia should be corrected prior to ondansetron administration.

Additional risk factors for Torsade de Pointes in the general population include, but are not limited to, the following:

- female gender;
- age 65 years or older;
- baseline prolongation of the QT/QTc interval;
- presence of genetic variants affecting cardiac ion channels or regulatory proteins;
- family history of sudden cardiac death at <50 years;
- cardiac disease (e.g., myocardial ischemia or infarction, left ventricular hypertrophy, cardiomyopathy, conduction system disease);
- history of arrhythmias (especially ventricular arrhythmias, atrial fibrillation, or recent conversion from atrial fibrillation);
- bradycardia (<50 beats per minute);
- acute neurological events (e.g., intracranial or subarachnoid haemorrhage, stroke, intracranial trauma);
- nutritional deficits (e.g., eating disorders, extreme diets);
- diabetes mellitus;
- autonomic neuropathy.

TEVA-ONDANSETRON and ONDANSETRON INJECTION (ondansetron hydrochloride) are not effective in preventing motion-induced nausea and vomiting.

Neurologic

Serotonin syndrome/Neuroleptic Malignant Syndrome: Cases of life-threatening serotonin syndrome or neuroleptic malignant syndrome-like events have been reported with 5-HT₃ receptor antagonist antiemetics, including ondansetron hydrochloride, when given in combination with other serotonergic and/or neuroleptic drugs. Serotonin syndrome symptoms may include mental status changes (e.g. agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g. nausea, vomiting, diarrhea). As these syndromes may result in potentially life-threatening conditions, treatment should be discontinued if such events occur and supportive symptomatic treatment should be initiated. If concomitant treatment of ondansetron hydrochloride with a drug affecting the serotonergic neurotransmitter system is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see **DRUG INTERACTIONS**).

Hepatic/Biliary/Pancreatic

There is no experience in patients who are clinically jaundiced. The clearance of an 8 mg intravenous dose of ondansetron hydrochloride was significantly reduced and the serum half-life significantly prolonged in subjects with severe impairment of hepatic function. In patients with moderate or severe

impairment of hepatic function, reductions in dosage are therefore recommended and a total daily dose of 8 mg should not be exceeded. This may be given as a single intravenous or oral dose.

Ondansetron does not itself appear to induce or inhibit the cytochrome P₄₅₀ drug-metabolizing enzyme system of the liver. Because ondansetron is metabolised by hepatic cytochrome P₄₅₀ drug-metabolizing enzymes; inducers or inhibitors of these enzymes may change the clearance and, hence, the half-life of ondansetron. On the basis of available data no dosage adjustment is recommended for patients on these drugs.

Gastrointestinal

As ondansetron is known to increase large bowel transit time, patients with signs of subacute intestinal obstruction should be monitored following administration.

Special Populations

Pregnant Women: The safety of ondansetron for use in human pregnancy has not been established. Ondansetron is not teratogenic in animals. However, as animal studies are not always predictive of human response, the use of ondansetron in pregnancy is not recommended.

Nursing Women: Ondansetron is excreted in the milk of lactating rats. It is not known if it is excreted in human milk, however, nursing is not recommended during treatment with ondansetron.

Pediatrics: (<3 years of age): Insufficient information is available to provide dosage recommendations for children 3 years of age or younger.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Ondansetron hydrochloride has been administered to over 2500 patients worldwide in controlled clinical trials and has been well tolerated.

The most frequent adverse events reported in controlled clinical trials were headache (11%) and constipation (4%). Other adverse events include sensations of flushing or warmth (<1%).

Cardiovascular:

There have been rare reports of tachycardia, angina (chest pain), bradycardia, hypotension, syncope and electrocardiographic alterations.

Central Nervous System:

There have been rare reports of seizures. Movement disorders and dyskinesia have been reported in two large clinical trials of ondansetron at a rate of 0.1 – 0.3%.

Dermatological:

Rash has occurred in approximately 1% of patients receiving ondansetron.

Eye Disorder:

Rare cases of transient visual disturbances (e.g. blurred vision) have been reported during or shortly after intravenous administration of ondansetron, particularly at rates equal to or greater than 30 mg in 15 minutes.

Hypersensitivity:

Rare cases of immediate hypersensitivity reactions sometimes severe, including anaphylaxis, bronchospasm, urticaria and angioedema have been reported.

Local Reactions:

Pain, redness and burning at the site of injection have been reported.

Metabolic:

There were transient increases of SGOT and SGPT of over twice the upper limit of normal in approximately 5% of patients. These increases did not appear to be related to dose or duration of therapy. There have been reports of liver failure and death in patients with cancer receiving concurrent medications including potentially hepatotoxic cytotoxic chemotherapy and antibiotics. The etiology of the liver failure is unclear. There have been rare reports of hypokalemia.

Other:

There have been reports of abdominal pain, weakness and xerostomia.

Post-Market Adverse Drug Reactions

Over 250 million patient treatment days of ondansetron hydrochloride have been supplied since the launch of the product worldwide. The following events have been spontaneously reported during post-approval use of ondansetron hydrochloride, although the link to ondansetron cannot always be clearly established.

The adverse event profiles in children and adolescents were comparable to that seen in adults.

Immune Disorders:

Rare cases of hypersensitivity reactions, sometimes severe (e.g., laryngeal edema, stridor, laryngospasm and cardiopulmonary arrest) have also been reported.

Cardiovascular Disorders:

There have been rare reports (<0.01%) of myocardial infarction, myocardial ischemia, angina, chest pain with or without ST segment depression, arrhythmias (including ventricular or supraventricular tachycardia, premature ventricular contractions, and atrial fibrillation), electrocardiographic alterations (including second degree heart block), palpitations and syncope.

Rarely and predominantly with intravenous ondansetron, transient ECG changes including QTc interval prolongation, Torsade de Pointes, ventricular fibrillation, cardiac arrest, and sudden death have been reported (see **WARNINGS AND PRECAUTIONS**, Cardiovascular).

Eye Disorder:

There have been very rare cases of transient blindness following ondansetron treatment, generally within the recommended dosing range and predominantly during intravenous administration.

The majority of blindness cases reported resolved within 20 minutes. Although most patients had received chemotherapeutic agents, including cisplatin a few cases of transient blindness occurred following ondansetron administration for the treatment of post-operative nausea or vomiting and in the absence of cisplatin treatment. Some cases of transient blindness were reported as cortical in origin.

Hepatobiliary Disorders:

Occasional asymptomatic increases in liver function tests have been reported.

Nervous System Disorders:

Transient episodes of dizziness (<0.1%) have been reported predominantly during or upon completion of IV infusion of ondansetron.

Uncommon reports (<1%) suggestive of extrapyramidal reactions including oculogyric crisis/dystonic reactions (e.g. oro-facial dyskinesia, opisthotonos, tremor, etc.), movement disorders and dyskinesia have been reported without definitive evidence of persistent clinical sequelae.

Serotonin syndrome and neuroleptic malignant syndrome-like events have been reported with 5-HT₃ receptor antagonist antiemetics, including ondansetron hydrochloride, when given in combination with other serotonergic and/or neuroleptic drugs (see **WARNINGS AND PRECAUTIONS**, Neurologic).

Respiratory, Thoracic and Mediastinal Disorders:

There have also been rare reports of hiccups.

Skin and Subcutaneous Tissue Disorders:

Very rare reports have been received for bullous skin and mucosal reactions, including fatal cases. These reports include toxic skin eruptions such as Stevens-Johnson syndrome and toxic epidermal necrolysis and have occurred in patients taking other medications that can be associated with bullous skin and mucosal reactions.

DRUG INTERACTIONS

Serious Drug Interactions

- **Apomorphine (see CONTRAINDICATIONS)**

Drug-Drug Interactions

Specific studies have shown that there are no pharmacokinetic interactions when ondansetron is administered with alcohol, temazepam, furosemide, tramadol or propofol.

Ondansetron is metabolised by multiple hepatic cytochrome P₄₅₀ enzymes: CYP3A4, CYP2D6 and CYP1A2. Despite the multiplicity of metabolic enzymes capable of metabolising ondansetron which can compensate for an increase or decrease in enzyme activity, it was found that patients treated with inducers of CYP3A4 (i.e. phenytoin, carbamazepine, and rifampicin) demonstrated an increase in oral clearance of ondansetron and a decrease in ondansetron blood concentrations. No effect in ondansetron clearance secondary to enzyme inhibition or reduced activity (e.g. CYP2D6 genetic deficiency) has been identified to date.

QTc-Prolonging Drugs: The concomitant use of ondansetron hydrochloride with another QTc-prolonging drug should be carefully considered to determine that the therapeutic benefit outweighs the potential risk. Drugs that have been associated with QTc interval prolongation and/or Torsade de Pointes include, but are not limited to, the examples in the following list. Chemical/pharmacological classes are listed if some, although not necessarily all, class members have been implicated in QTc prolongation and/or Torsade de Pointes:

- Class IA antiarrhythmics (e.g., quinidine, procainamide, disopyramide);
- Class III antiarrhythmics (e.g., amiodarone, sotalol, ibutilide, dronedarone);
- Class IC antiarrhythmics (e.g., flecainide, propafenone);
- antiemetics (e.g., dolasetron, droperidol, chlorpromazine, prochlorperazine);
- tyrosine kinase inhibitors (e.g., vandetanib, sunitinib, nilotinib, lapatinib);
- antipsychotics (e.g., chlorpromazine, pimozide, haloperidol, ziprasidone);
- antidepressants (e.g., citalopram, fluoxetine, venlafaxine, tricyclic/tetracyclic antidepressants e.g., amitriptyline, imipramine, maprotiline);
- opioids (e.g., methadone);
- domperidone
- macrolide antibiotics and analogues (e.g., erythromycin, clarithromycin, telithromycin, tacrolimus);
- quinolone antibiotics (e.g., moxifloxacin, levofloxacin, ciprofloxacin);
- antimalarials (e.g., quinine, chloroquine);
- azole antifungals (e.g., ketoconazole, fluconazole, voriconazole);
- histone deacetylase inhibitors (e.g., vorinostat);
- beta-2 adrenoceptor agonists (e.g., salmeterol, formoterol).

Drugs that Cause Electrolyte Abnormalities:

The use of ondansetron hydrochloride with drugs that can disrupt electrolyte levels should be avoided. Such drugs include, but not limited to, the following:

- loop, thiazide, and related diuretics;
- laxatives and enemas;
- amphotericin B;
- high dose corticosteroids.

The above lists of potentially interacting drugs are not comprehensive. Current information sources should be consulted for newly approved drugs that prolong the QTc interval or cause electrolyte disturbances, as well as for older drugs for which these effects have recently been established.

Tramadol:

Data from small studies indicate that ondansetron may reduce the analgesic effect of tramadol.

Apomorphine:

Based on reports of profound hypotension and loss of consciousness when ondansetron was administered with apomorphine hydrochloride, concomitant use with apomorphine is contraindicated (see **CONTRAINDICATIONS**).

Serotonergic Drugs:

As with other serotonergic agents, serotonin syndrome, a potentially life-threatening condition, may occur with 5-HT₃ receptor antagonist antiemetic treatment when given in combination with other agents that may affect the serotonergic neurotransmitter system (including triptans, SSRIs, SNRIs, lithium, sibutramine, fentanyl and its analogues, dextromethorphan, tramadol, tapentadol, meperidine, methadone, and pertazocine or St. John's Wort (*Hypericum perforatum*), and with drugs which impair metabolism of serotonin (such as MAOIs, including linezolid (an antibiotic which is a reversible non-selective MAOI), and methylene blue; see **WARNINGS AND PRECAUTIONS**, Neurologic)

DOSAGE AND ADMINISTRATION

Dosing Considerations

Ondansetron Hydrochloride has a dose dependent QTc prolongation effect. For IV administration, the effect is expected to be greater with a faster rate of infusion. Using the minimum effective dose and a slow rate of infusion should always be favoured.

Recommended Dose and Dosage Adjustment

Chemotherapy Induced Nausea and Vomiting:

Use in Adults:

Highly Emetogenic Chemotherapy (e.g. regimens containing cisplatin)

Initial Dose for Prevention of Emesis during the First 24 h Following Chemotherapy:

ONDANSETRON INJECTION (ondansetron hydrochloride) should be given as an initial dose prior to chemotherapy, followed by a dosage regimen tailored to the anticipated severity of emetic response caused by different cancer treatments. The usual dose is ONDANSETRON INJECTION 8 mg infused intravenously over 15 minutes given at least 30 minutes prior to chemotherapy. A maximum initial dose of ONDANSETRON INJECTION 16 mg IV infused over 15 minutes may be used. A single IV dose greater than 16 mg should not be given due to the dose dependent risk of QTc prolongation. The QTc prolongation effect of ONDANSETRON INJECTION is also expected to be

greater if the drug is administered rapidly. Do not administer more rapidly than the recommended 15 minute infusion (see **WARNINGS AND PRECAUTIONS**, General, QTc Interval Prolongation; **DRUG INTERACTIONS**, Drug-Drug Interactions, QTc-Prolonging Drugs; **ACTION AND CLINICAL PHARMACOLOGY**, Electrocardiography).

IV doses greater than 8 mg and up to a maximum of 16 mg must be diluted in 50 mL to 100 mL of 0.9% Sodium Chloride Injection or 5% Dextrose Injection before administration and infused over not less than 15 minutes. IV doses of 8 mg or less do not need to be diluted and may be administered as an IV injection over 15 minutes.

Post-chemotherapy:

Two additional doses of ONDANSETRON INJECTION 8 mg IV (15 minutes infusions) may be given 4 and 8 hours after the initial dose of ONDANSETRON INJECTION.

After the first 24 hours, TEVA-ONDANSETRON 8 mg may be taken orally every 8¹ hours for up to 5 days.

Less Emetogenic Chemotherapy (e.g. regimens containing cyclophosphamide, doxorubicin, epirubicin, fluorouracil and carboplatin)

Initial Dose:

ONDANSETRON INJECTION 8 mg infused intravenously over 15 minutes, given at least 30 minutes prior to chemotherapy; or TEVA-ONDANSETRON 8 mg orally 1 to 2 hours prior to chemotherapy.

Post-chemotherapy:

TEVA-ONDANSETRON 8 mg orally twice daily for up to 5 days.

Use in Children:

Clinical experience of ondansetron hydrochloride for the treatment of Post-Chemotherapy Induced Nausea and Vomiting in children is currently limited, however, ondansetron hydrochloride was effective and well tolerated when given to children 4-12 years of age. ONDANSETRON INJECTION should be given intravenously at a dose of 3-5 mg/m² over 15 minutes at least 30 minutes before chemotherapy. After therapy, TEVA-ONDANSETRON 4 mg should be given orally every 8 hours¹ for up to 5 days. For children 3 years of age and younger, there is insufficient information available to make dosage recommendations, therefore TEVA-ONDANSETRON and ONDANSETRON INJECTION are not indicated for the treatment of children 3 years of age or younger (see **INDICATIONS AND CLINICAL USE**).

Use in Elderly:

Oral Formulation:

Efficacy and tolerance in patients aged over 65 years were similar to that seen in younger adults indicating no need to alter oral dosage schedules in this population.

¹ The efficacy of twice daily dosage regimens for the treatment of post-chemotherapy emesis has been established only in adult patients receiving less emetogenic chemotherapy. The appropriateness of twice versus three times daily dosage regimens for other patient groups should be based on an assessment of the needs and responsiveness of the individual patient.

IV Formulation:

In patients 65 years of age or older, all IV doses should be diluted in 50 mL to 100 mL of 0.9% Sodium Chloride Injection or 5% Dextrose Injection.

In patients 65 to 74 years of age, the initial IV dose of ONDANSETRON INJECTION 8 mg or 16 mg, infused over 15 minutes, may be followed by 2 doses of 8 mg infused over 15 minutes and given no less than 4 hours apart. When the initial dose is 16 mg, there is a predicted increase of the risk for a slight QTcF interval prolongation above 10 ms (from baseline) for about 10 min. ECG monitoring may be considered.

In patients 75 years of age or older, the initial IV dose of ONDANSETRON INJECTION should not exceed 8 mg infused over 15 minutes. The initial dose of 8 mg may be followed by 2 doses of 8 mg, infused over 15 minutes and given no less than 4 hours apart. For the third dose, there is a predicted increase of the risk for a slight QTcF interval prolongation above 10 ms (from baseline) for about 10 min. ECG monitoring may be considered.

Radiotherapy Induced Nausea and Vomiting:

Use in Adults:

Initial Dose

TEVA-ONDANSETRON 8 mg orally 1 to 2 hours before radiotherapy.

Post-radiotherapy

TEVA-ONDANSETRON 8 mg orally every 8 hoursⁱ for up to 5 days after a course of treatment.

Use in Children:

There is no experience in clinical studies in this population. TEVA-ONDANSETRON and ONDANSETRON INJECTION are not indicated for the prevention and treatment of radiotherapy induced nausea and vomiting in children (see **INDICATIONS AND CLINICAL USE**).

Use in Elderly:

Efficacy and tolerance in patients aged over 65 years were similar to that seen in younger adults indicating no need to alter dosage schedules in this population.

Post-Operative Nausea and Vomiting:

Use in Adults:

For prevention of post-operative nausea and vomiting TEVA-ONDANSETRON may be administered as a single dose of 16 mg given orally one hour prior to anaesthesia.

Alternatively, a single dose of 4 mg, undiluted may be injected intravenously preferably over 2-5 minutes, and not less than 30 seconds, at induction of anaesthesia.

For the treatment of established post-operative nausea and vomiting, a single dose of 4 mg, undiluted injected intravenously preferably over 2-5 minutes, and not less than 30 seconds, is recommended.

Use in Children:

There is no experience in the use of ondansetron hydrochloride in the prevention and treatment of post-operative nausea and vomiting in children; TEVA-ONDANSETRON and ONDANSETRON INJECTION are not indicated for this use in children (see **INDICATIONS AND CLINICAL USE**).

Use in Elderly:

There is limited experience in the use of ondansetron hydrochloride in the prevention and treatment of post-operative nausea and vomiting in the elderly; TEVA-ONDANSETRON and ONDANSETRON INJECTION are not indicated for this use in the elderly (see **INDICATIONS AND CLINICAL USE**).

Patients with Renal/Hepatic Impairment:***Use in Patients with Impaired Renal Function:***

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

Use in Patients with Impaired Hepatic Function:

The clearance of an 8 mg intravenous dose of ondansetron hydrochloride was significantly reduced and the serum half-life significantly prolonged in subjects with severe impairment of hepatic function. In patients with moderate or severe impairment of hepatic function, reductions in dosage are therefore recommended and a total daily dose of 8 mg should not be exceeded. This may be given as a single intravenous or oral dose.

No studies have been conducted to date in patients with jaundice.

Patients with Poor Sparteine/Debrisoquine Metabolism:

The elimination half-life and plasma levels of a single 8 mg intravenous dose of ondansetron did not differ between subjects classified as poor and extensive metabolisers of sparteine and debrisoquine. No alteration of daily dosage or frequency of dosing is recommended for patients known to be poor metabolisers of sparteine and debrisoquine.

Administration**Administration of Intravenous Infusion Solutions*****Compatibility with Intravenous Solutions:***

ONDANSETRON INJECTION is compatible with the following solutions:

ONDANSETRON INJECTION (Preservative-Free - 2 mL and 4 mL Vials):

- 0.9% w/v Sodium Chloride Injection
- 5% w/v Dextrose Injection
- 10% w/v Mannitol Injection
- Ringers Injection
- 0.3% w/v Potassium Chloride and 0.9% w/v Sodium Chloride Injection
- 0.3% w/v Potassium Chloride and 5% w/v Dextrose Injection

ONDANSETRON INJECTION (Preservative - 20 mL Vials):

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

Compatibility with Other Drugs:

ONDANSETRON INJECTION should not be administered in the same syringe or infusion with any other medication. ONDANSETRON INJECTION may be administered by intravenous infusion at 1 mg/hour (e.g. from an infusion bag or syringe pump).

The following drugs may be administered via the Y-site of the administration set, for ondansetron concentrations of 16 to 160 µg/mL. If the concentrations of cytotoxic drugs required are higher than indicated below, they should be administered through a separate intravenous line.

For ONDANSETRON INJECTION - Preservative-Free and Preservative:

Cisplatin - concentrations up to 0.48 mg/mL administered over 1 to 8 hours.

For ONDANSETRON INJECTION - Preservative-Free:

5-Fluorouracil - concentrations up to 0.8 mg/mL, administered at rates of at least 20 mL/hour.

Higher concentrations of 5-fluorouracil may cause precipitation of ondansetron. The 5-fluorouracil infusion may contain up to 0.045% w/v magnesium chloride.

Carboplatin - concentrations of 0.18 mg/mL - 9.9 mg/mL, administered over 10 - 60 minutes.

Ceftazidime - bolus IV doses, over approximately 5 minutes, of 250 - 2000 mg reconstituted with Water for Injections BP.

Cyclophosphamide - bolus IV doses over approximately 5 minutes, of 100 - 1000 mg, reconstituted with Water for Injections BP 5 mL per 100 mg cyclophosphamide.

Doxorubicin and Epirubicin - bolus IV doses over approximately 5 minutes of 10-100 mg as a 2 mg/mL solution. Lyophilized powder presentations can be reconstituted with 0.9% Sodium Chloride Injection USP.

Etoposide - concentrations of 0.144 mg/mL - 0.25 mg/mL, administered over 30 - 60 minutes.

OVERDOSAGE

For management of a suspected drug overdose contact your regional Poison Control Centre.
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At present there is little information concerning overdosage with ondansetron. Individual doses of 84 mg and 145 mg and total daily doses as large as 252 mg have been administered with only mild side

effects. There is no specific antidote for ondansetron, therefore, in cases of suspected overdose, symptomatic and supportive therapy should be given as appropriate.

Further management should be as clinically indicated or as recommended by the regional Poison Control Centre, where available.

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

“Sudden blindness” (amaurosis) of 2 to 3 minutes duration plus severe constipation occurred in one patient that was administered 72 mg of ondansetron intravenously as a single dose. Hypotension (and faintness) occurred in another patient that took 48 mg of oral ondansetron. Following infusion of 32 mg over only a 4-minute period, a vasovagal episode with transient second degree heart block was observed. Neuromuscular abnormalities, autonomic instability, somnolence, and a brief generalized tonic-clonic seizure (which resolved after a dose of benzodiazepine) were observed in a 12-month-old infant who ingested seven or eight 8-mg ondansetron tablets (approximately forty times the recommended 0.1-0.15 mg/kg dose for a pediatric patient). In all instances, the events resolved completely.

Ondansetron prolongs QT interval in a dose-dependent fashion (see **ACTION AND CLINICAL PHARMACOLOGY**, Pharmacodynamics). ECG monitoring is recommended in cases of overdose.

Cases consistent with serotonin syndrome have been reported in young children following oral overdose.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Ondansetron hydrochloride is a selective antagonist of the serotonin receptor subtype, 5-HT₃. Its precise mode of action in the control of chemotherapy induced nausea and vomiting is not known.

Cytotoxic chemotherapy and radiotherapy are associated with the release of serotonin (5-HT) from enterochromaffin cells of the small intestine, presumably initiating a vomiting reflex through stimulation of 5-HT₃ receptors located on vagal afferents. Ondansetron may block the initiation of this reflex. Activation of vagal afferents may also cause a central release of serotonin from the chemoreceptor trigger zone of the *area postrema*, located on the floor of the fourth ventricle. Thus, the antiemetic effect of ondansetron is probably due to the selective antagonism of 5-HT₃ receptors on neurons located in either the peripheral or central nervous systems, or both.

The mechanisms of ondansetron’s antiemetic action in post-operative nausea and vomiting are not known.

Pharmacodynamics

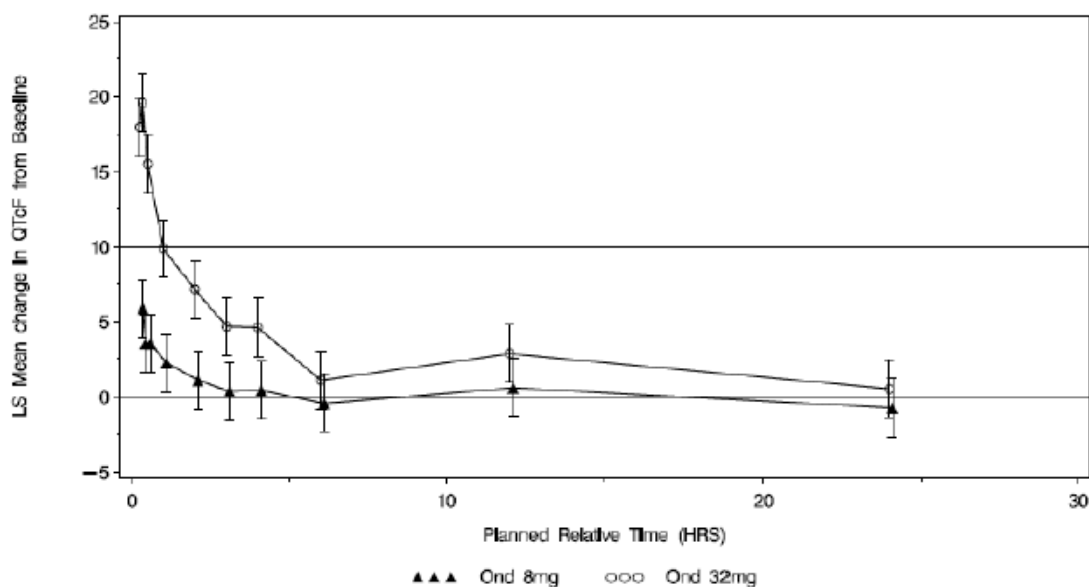
In vitro metabolism studies have shown that ondansetron is a substrate for human hepatic cytochrome P₄₅₀ enzymes, including CYP1A2, CYP2D6 and CYP3A4. In terms of overall ondansetron turnover, CYP3A4 played the predominant role. Because of the multiplicity of metabolic enzymes capable of metabolising ondansetron, it is likely that inhibition or loss of one enzyme (e.g. CYP2D6 enzyme deficiency) will be compensated by others and may result in little change in overall rates of ondansetron clearance.

Electrocardiography

The effect of ondansetron on the QTc interval was evaluated in a double blind, randomized, placebo and positive (moxifloxacin) controlled, crossover study in 58 healthy adult men and women. Ondansetron was tested at single doses of 8 mg and 32 mg infused intravenously over 15 minutes. At the highest tested dose of 32 mg, prolongation of the Fridericia-corrected QTc interval $QT/RR^{0.33}=QTcF$ was observed from 15 min to 4 h after the start of the 15 min infusion, with a maximum mean (upper limit of 90% CI) difference in QTcF from placebo after baseline-correction of 19.6 (21.5) msec at 20 min. At the lower tested dose of 8 mg, QTc prolongation was observed from 15 min to 1 h after the start of the 15 minute infusion, with a maximum mean (upper limit of 90% CI) difference in QTcF from placebo after baseline-correction of 5.8 (7.8) msec at 15 min. The magnitude of QTc prolongation with ondansetron is expected to be greater if the infusion rate is faster than 15 minutes. The 32 mg intravenous dose of ondansetron must not be administered.

No treatment-related effects on the QRS duration or the PR interval were observed at either the 8 or 32 mg dose.

LS Mean Difference (90% CI) in QTcF Interval between Treatment and Placebo Over Time



An ECG assessment study has not been performed for orally administered ondansetron hydrochloride. On the basis of pharmacokinetic-pharmacodynamic modelling, an 8 mg oral dose of

ondansetron hydrochloride is predicted to cause a mean QTcF increase of 0.7 ms (90% CI -2.1, 3.3) at steady-state, assuming a mean maximal plasma concentration of 24.7 ng/mL (95% CI 21.1, 29.0).

The magnitude of QTc prolongation at the recommended 5 mg/m² dose in pediatrics has not been studied, but pharmacokinetic-pharmacodynamic modelling predicts a mean increase of 6.6 ms (90% CI 2.8, 10.7) at maximal plasma concentrations.

Pharmacokinetics

Pharmacokinetic studies in human volunteers showed peak plasma levels of 20-30 ng/mL at around 1½ hours after an 8 mg oral dose of ondansetron. An 8 mg infusion of ondansetron resulted in peak plasma levels of 80-100 ng/mL. Repeat dosing of an 8 mg tablet every 8 hours for 6 days increased the peak plasma value to 40 ng/mL. A continuous intravenous infusion of 1 mg/hour after the initial 8 mg loading dose of ondansetron maintained plasma levels over 30 ng/mL during the following 24 hour period.

The absolute bioavailability of ondansetron in humans was approximately 60% and the plasma protein binding was approximately 73%.

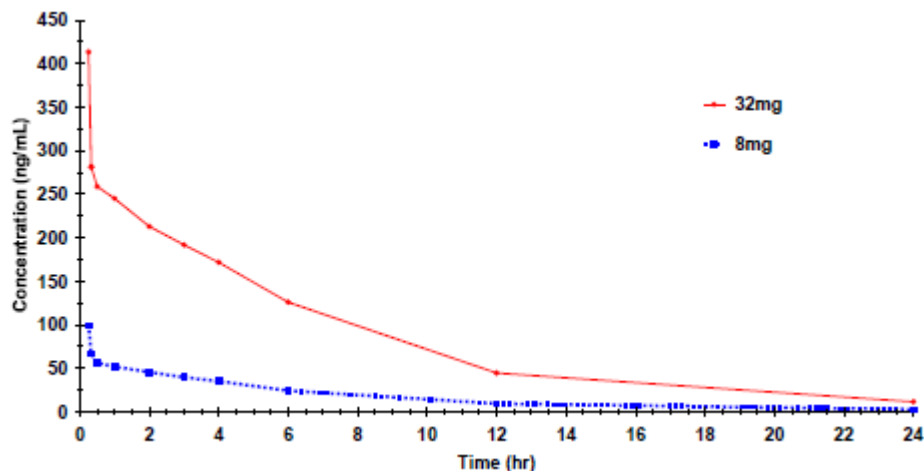
Following oral or IV administration, ondansetron is extensively metabolised and excreted in the urine and faeces. In humans, less than 10% of the dose is excreted unchanged in the urine. The major urinary metabolites are glucuronide conjugates (45%), sulphate conjugates (20%) and hydroxylation products (10%).

The half-life of ondansetron after either an 8 mg oral dose or intravenous dose was approximately 3-4 hours and may be extended to 6-8 hours in the elderly.

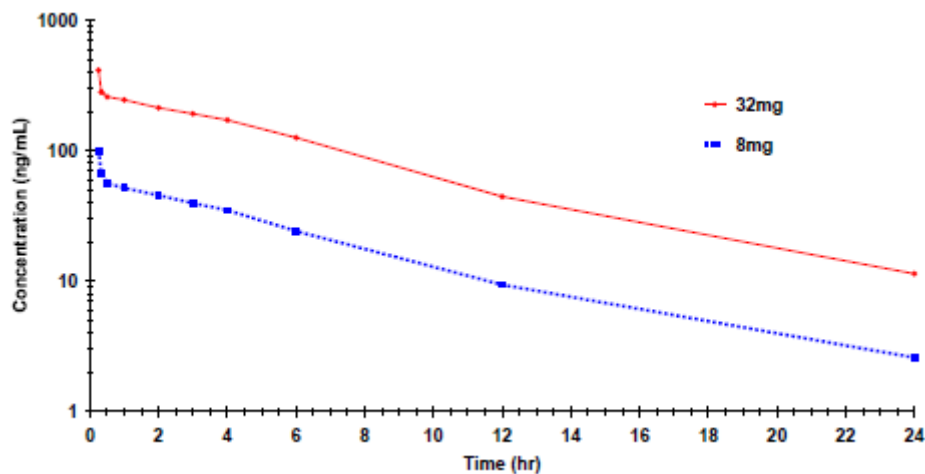
Mean plasma concentration-time curves for ondansetron following 8 mg and 32 mg dose are shown below:

Mean Plasma Concentration-Time Curve for Ondansetron 8mg and 32 mg IV doses

Linear Scale



Semi-logarithmic Scale



In a pharmacokinetic study of 16 epileptic patients maintained chronically on carbamazepine or phenytoin, reduction in AUC, C_{max} and $T_{1/2}$ of ondansetron was observed. This resulted in a significant increase in clearance. However, on the basis of the inter-subject variability in the available data, no dosage adjustment can be recommended (see **DRUG INTERACTIONS**, Drug-Drug Interactions).

Early Phase I studies in healthy elderly volunteers showed a slight age-related decrease in clearance, and an increase in half-life of ondansetron. However, wide inter-subject variability resulted in considerable overlap in pharmacokinetic parameters between young (< 65 years of age) and elderly subjects (≥ 65 years of age) and there were no overall differences in safety or efficacy observed between young and elderly cancer patients enrolled in CINV clinical trials (see **DOSAGE AND ADMINISTRATION**, Use in Elderly).

Based on more recent ondansetron plasma concentrations and exposure-response modeling, a greater effect on QTcF is predicted in patients ≥ 75 years of age compared to young adults. Specific dosing information is provided for patients over 65 years of age and over 75 years of age for intravenous dosing (see **DOSAGE AND ADMINISTRATION**, Use in Elderly).

STORAGE AND STABILITY

TEVA- ONDANSETRON Tablets should be stored between 15°C and 30°C.

ONDANSETRON INJECTION should be stored between 15°C and 30°C. ONDANSETRON INJECTION should not be frozen and should be protected from light. ONDANSETRON INJECTION must not be autoclaved.

The preservative-free ONDANSETRON INJECTION (2 mL and 4 mL vials) are for single use and unused portions of these vials should be discarded.

The 20 mL vials are multiple dose vials and should be discarded 28 days after initial puncture.

Stability and Storage of Diluted Solutions:

Compatibility studies have been undertaken in polyvinyl chloride infusion bags. Intravenous solutions should be prepared at the time of infusion. ONDANSETRON INJECTION, preservative and preservative-free, when diluted with the recommended intravenous solutions, should be used within 24 hours if stored at room temperature or used within 72 hours if stored in a refrigerator, due to possible microbial contamination during preparation.

As with all parenteral drug products, intravenous admixtures should be inspected visually for clarity, particulate matter, precipitate, discoloration and leakage prior to administration, whenever solution and container permit. Solutions showing haziness, particulate matter, precipitate, discoloration or leakage should not be used. Discard unused portion.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms, Composition and Packaging

TEVA-ONDANSETRON Tablets

TEVA-ONDANSETRON tablets contain either 4 mg or 8 mg of ondansetron base, in the form of ondansetron hydrochloride dihydrate. TEVA-ONDANSETRON tablets also contain the following excipients: lactose monohydrate, magnesium stearate, microcrystalline cellulose, pregelatinized starch, sodium starch glycolate, and film-coating containing: hypromellose, hydroxypropyl methylcellulose, iron oxide yellow, macrogol, polyethylene glycol, polysorbate and titanium dioxide.

TEVA-ONDANSETRON 4 mg tablets:

Yellow, oval shaped, film-coated tablets, engraved with "N" on one side and "4" on the other side. Each tablet contains 4 mg ondansetron (as ondansetron hydrochloride dihydrate). Available in blister packages of 10 tablets.

TEVA-ONDANSETRON 8 mg tablets:

Yellow, oval shaped, film-coated tablets, engraved with "N" on one side and "8" on the other side. Each tablet contains 8 mg ondansetron (as ondansetron hydrochloride dihydrate). Available in child resistant white high density polyethylene bottles of 100 tablets and blister packages of 10 tablets.

ONDANSETRON INJECTION

ONDANSETRON INJECTION contains 2 mg/mL of ondansetron base, in the form of ondansetron hydrochloride dihydrate.

Each mL of ONDANSETRON INJECTION (Preservative-Free - 2 mL and 4 mL Vials) also contains: citric acid monohydrate 0.50 mg, sodium chloride 9.00 mg, sodium citrate dehydrate 0.25 mg and Water for Injection.

Each mL of ONDANSETRON INJECTION (Preservative - 20 mL vial) also contains: citric acid monohydrate 0.50 mg, methylparaben 1.2 mg, propylparaben 0.15 mg, sodium chloride 8.3 mg, sodium citrate dehydrate 0.25 mg and Water for Injection.

ONDANSETRON INJECTION 2 mg/mL (as ondansetron hydrochloride dihydrate) for intravenous use is supplied as follows:

- preservative-free 2 mL (4 mg) vials, in cartons of 10 vials
- preservative-free 4 mL (8 mg) vials, in cartons of 5 vials
- preservative 20 mL (40 mg) vials, packed in individual cartons

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

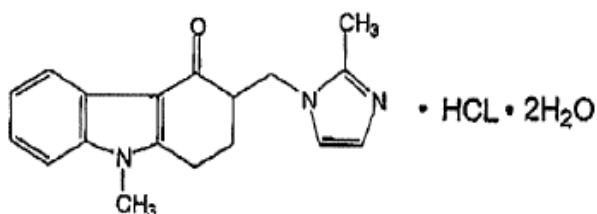
Common Name: ondansetron hydrochloride dihydrate

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

Molecular Formula: C₁₈H₁₉N₃O·HCl·2H₂O (hydrochloride dihydrate)

Molecular Weight: 365.87

Structural Formula:



Physicochemical Properties:

Description and Solubility: Ondansetron hydrochloride dihydrate is a white or almost white powder. It is sparingly soluble in water and alcohol, soluble in methanol, slightly soluble in methylene chloride. The melting point of ondansetron hydrochloride dihydrate is 178.5°C to 179.5°C. pKa is 7.4. The natural pH of ondansetron hydrochloride solution is 4.1 to 4.5.

CLINICAL TRIALS

Comparative Bioavailability Study

A comparative, two-way, single-dose, bioavailability study was performed in 26 healthy adult subjects under fasting conditions on TEVA-ONDANSETRON (ondansetron hydrochloride) 8 mg tablets and Zofran[®] 8 mg tablets by GlaxoSmithKline, UK. The pharmacokinetic data calculated for the two ondansetron formulations are tabulated below:

TABLE OF COMPARATIVE BIOAVAILABILITY DATA

Ondansetron (1 x 8 mg) From measured data				
Geometric Mean Arithmetic Mean (CV%)				
Parameters	Teva-Ondansetron Tablets*	Zofran [®] † Tablets	Ratio of Geometric Means (%)	90% Confidence Interval
AUC _{0-t} (ng·h/mL)	235.09 247.74 (31.49)	233.44 247.63 (33.00)	100.71	96.53 % to 105.07 %
AUC _{0-inf} (ng·h/mL)	247.07 261.57 (33.97)	245.18 261.70 (36.15)	100.77	96.45 % to 105.28 %
C _{max} (ng/mL)	35.84 37.34 (28.52)	35.29 37.11 (31.52)	101.56	94.73 % to 108.88 %
T _{max} § (h)	1.64 (37.29)	1.73 (35.13)	-	-
T _{1/2 el} § (h)	5.36 (18.04)	5.36 (19.19)	-	-

*Teva-Ondansetron 8 mg tablets (Teva Canada Limited, Canada).

†Zofran[®] 8 mg Tablets, GlaxoSmithKline, Middlesex, UK; purchased in the UK.

§expressed as arithmetic mean (CV%) only.

Study results

Clinical trial results showing the number and percentage of patients exhibiting a complete response to ondansetron (0 emetic episodes) are shown in the tables below for both post-operative and chemotherapy induced emesis.

Prevention of Chemotherapy Induced Emesis – Response over 24 Hours

Dose	Ondansetron hydrochloride* 3 doses of 0.15 mg/kg	Placebo* 3 doses of placebo	Ondansetron hydrochloride 8 mg IV + 1 mg/hr, 24 hours	Ondansetron hydrochloride 8 mg IV	Ondansetron hydrochloride 32 mg IV
# of patients	14	14	168	152	173
Treatment Response					
0 emetic episodes	2 (14%)	0 (0%)	92 (55%)	82 (54%)	97 (56%)
1-2 emetic episodes	8 (57%)	0 (0%)	-	-	-

* Results are from an initial study using a different dosing regimen

Prevention of Post-Operative Emesis – Response Over 24 Hours *

Dose	Oral Prevention			Intravenous Prevention		
	Ondansetron hydrochloride 16 mg OD	Placebo	p-value	Ondansetron hydrochloride 4 mg IV	Placebo	p-value
# of patients	253	250		136	139	
Treatment Response						
0 emetic episodes	126 (50%)	79 (32%)	<0.001	103 (76%)	62 (46%)	<0.001

* The majority of patients included in the prevention and treatment of post-operative nausea and vomiting studies using ondansetron hydrochloride have been adult women receiving balanced anaesthesia for gynaecological surgery.

Treatment of Post-Operative Emesis – Response over 24 Hours*

Dose	Intravenous Treatment		
	Ondansetron hydrochloride 4 mg IV	Placebo	p-value
# of patients	104	117	
Treatment Response			
0 emetic episodes	49 (47%)	19 (16%)	<0.001

* The majority of patients included in the prevention and treatment of post-operative nausea and vomiting studies using ondansetron hydrochloride have been adult women receiving balanced anaesthesia for gynaecological surgery.

Prevention of Radiotherapy Induced Emesis – Response over 24 Hours*

Dose	Oral Treatment		
	Ondansetron hydrochloride 8 mg PO tid**	Metoclopramide 10 mg PO tid**	p-value
# of patients	38	44	
Treatment Response			
0 emetic episodes	37 (97%)	20 (45%)	<0.001

* Results from a study of adult male and female patients receiving single high dose radiotherapy (800 to 1,000 cGy) over an anterior or posterior field size of ≥ 80 cm² to the abdomen.

**Patients received the first dose of ondansetron hydrochloride 8 mg tablets or metoclopramide (10 mg) 1-2 hours before radiotherapy. If radiotherapy was given in the morning, 2 additional doses of study treatment were given (1 tablet late afternoon and 1 tablet before bedtime). If radiotherapy was given in the afternoon, patients took only 1 further tablet that day before bedtime. Patients continued oral medication on a 3 times a day basis for 3-5 days.

DETAILED PHARMACOLOGY

Animal Pharmacology

Pharmacodynamics :

The ferret provides an excellent model for demonstrating the antiemetic action of drugs. Emesis can be induced by antineoplastic drugs or whole body irradiation. Behavioural changes associated with these treatments are noted in these animals and may also provide a parallel for the human experience of nausea.

The antiemetic action of ondansetron has been evaluated in both male and female ferrets given cisplatin (9-10 mg/kg), cyclophosphamide (200 mg/kg) or irradiation (2 and 8 Gy, 250 kV). Intravenous doses of ondansetron (0.1-1 mg/kg) abolished cisplatin-induced emesis for up to 2 hours. In cyclophosphamide-induced emesis, subcutaneous doses of 0.5 mg/kg ondansetron completely eliminated vomiting, significantly reduced retching and delayed the onset of these responses.

The radiation-induced emesis, 0.5 mg/kg ondansetron alone completely and rapidly eliminated retching and vomiting.

Serotonin receptors of the 5-HT₃ type are present both peripherally and on vagal nerve terminals. Ondansetron probably acts by preventing activation of these receptors or receptors located in other regions of the central nervous system. Both the peripheral and central nervous systems appear to be involved since both abdominal vagotomy and microinjection of ondansetron and other 5-HT₃ antagonists directly into the area postrema eliminate cisplatin-induced emesis, while 5-HT₁-like (methiothepin maleate) and 5-HT₂ (ketanserin) antagonists have no effect.

Ondansetron is highly selective for 5-HT₃ receptors and shows negligible binding to other receptors such as 5-HT₁-like, 5-HT₂, α 1 and α 2 adrenoceptors, β 1 and β 2 adrenoceptors, D₁ and D₂ muscarinic, nicotinic, GABA_A, H₁ and H₂ receptors.

The pharmacological specificity of ondansetron may explain the observed lack of extrapyramidal side effects often seen following similar therapy with metoclopramide, which preferentially binds to dopamine receptors of the D₂ subtype.

Among its secondary effects, ondansetron has also been shown to cause a dose-dependent increase in the rate of gastric emptying in the guinea pig which is significant at doses of 0.01-0.1 mg/kg. As gastric stasis is frequently associated with nausea, stimulation of gastric motility may be a beneficial action of ondansetron. In the cat, dog and monkey, ondansetron has little effect on heart rate, blood pressure or ECG at intravenous doses up to 3 mg/kg.

A study in cloned human cardiac ion channels has shown ondansetron has the potential to affect cardiac repolarisation via blockade of hERG potassium channels at clinically relevant concentrations. Dose-dependent QT prolongation has been observed in a thorough QT study in human volunteers (see **ACTION AND CLINICAL PHARMACOLOGY** - Pharmacodynamics – Electrocardiography).

Pharmacokinetics :

In mice, rats, rabbits and dogs dosed at 1 mg/kg orally and/or intravenously, the plasma half-life of ondansetron was less than 1 hour, but the half-lives of its metabolites were significantly longer. Peak plasma concentrations of ondansetron in rats and dogs ranged from 351 to 419 ng/mL for the IV dose and 8 to 15 ng/mL for the oral dose. Plasma levels were linear over a 30 fold dose range. In repeat dose studies there was no apparent accumulation of ondansetron.

Ondansetron is almost completely absorbed in animals, and is rapidly metabolized by N-demethylation and hydroxylation of the indole ring, followed by conjugation with glucuronic acid and sulphate. There is significant first-pass metabolism after oral doses.

Ondansetron and its metabolites are rapidly and widely distributed in tissues, reaching higher levels than the corresponding plasma levels. In the rat and dog, ondansetron binds reversibly to tissues containing melanin and elastin. In rats and man, plasma protein binding is about 73%, while it is slightly lower in the dog (60%). Ondansetron and its metabolites cross the blood-brain barrier to only a slight extent.

Human Pharmacology

Pharmacodynamics:

In vivo pharmacodynamic studies have investigated the effects of ondansetron on gastric emptying, small bowel transit time and oesophageal motility.

Both oral (16 mg tid) and intravenous (5-10 mg) doses of ondansetron failed to produce a significant effect on gastric emptying in both healthy volunteers and in patients suffering from delayed gastric emptying. However, in one study intravenous doses of 8 mg did increase gastric emptying in over half the volunteers tested.

Intravenous infusion of either 1 mg or 5 mg ondansetron tended to increase small bowel transit times and single intravenous doses of 10 mg ondansetron have been reported to decrease sphincter pressure in the lower oesophagus in some subjects.

In psychomotor testing ondansetron does not impair performance nor cause sedation.

MICROBIOLOGY

Not applicable.

TOXICOLOGY

Acute Toxicity:

Single doses of ondansetron up to the LD₅₀ in mice and in rats were generally well tolerated. Reactions, including tremor and convulsive behaviour, occurred only at near lethal levels.

Species	LD ₅₀ (mg/kg)	
	Oral	IV
Mice	10-30	1.0-2.5
Rats	100-150	15-20

All deaths resulted from the acute effects of treatment, the observed clinical signs being consistent with the central nervous system effects associated with behavioural depression. These effects were not associated with any apparent histopathological changes in the brain. No target organ toxicity was identified.

Long term Toxicity:

Subacute Toxicity Studies

Species	Route	Dose (mg/kg/day)	Duration of Study	Results
Rats	Oral	160	7 weeks	Well tolerated
	IV	12	5 weeks	Well tolerated
Dogs	Oral	7.5 – 25	5 weeks	Transient post-dosing clinical reactions associated with behavioural depression (at highest dose levels)
	IV	2 - 8	5 weeks	

Maximum daily dose levels in rats were found to be higher when doses were gradually increased. Identical doses were rapidly lethal to rats not previously exposed to ondansetron. Post-dosing reactions, in both rats and dogs, included ataxia, exophthalmia, mydriasis, tremor and respiratory changes. Increases in liver enzymes (SGPT and SGOT) were noted at high dose levels. Dogs dosed at 6.75 mg/kg/day intravenously exhibited vein irritancy in the form of constriction and thickening, creating resistance to needle penetration. The changes were noted after seven days treatment but were reversed by decreasing the dose concentration.

Chronic Toxicity

Species	Duration	Max. no-effect Dose (mg/kg/day)	Effects
Rat	18 months	1	Usually transient and restricted to highest dose
Dog	12 months	12	

Carcinogenicity Studies

Species	Route	Dose (mg/kg/day)	Duration of Study	Results
Mice	Oral	1-40 (max. oral dose 30)	2 years	No treatment related increases in tumour incidence.
Rats	Oral	1-25 (max. oral dose 10)	2 years	Proportion of benign/malignant tumours also remained consistent with the pathological background of the animals studied.

There was no evidence of a tumourigenic effect of ondansetron in any tissue.

Mutagenicity Studies:

No evidence of mutagenicity was observed in microbial mutagen tests using mutant strains of *Salmonella typhimurium*, *Escherichia coli* or *Saccharomyces cerevisiae*, with or without a rat-liver post-mitochondrial metabolizing system.

There was also no evidence of damage to genetic material noted in *in vitro* V-79 mammalian cell mutation studies, *in vitro* chromosome aberration tests using human peripheral lymphocytes, or *in vivo* chromosome aberration assays in mouse bone marrow.

Reproduction and Teratology:

Ondansetron was not teratogenic in rats and rabbits at dosages up to the maximum non-convulsive level, (rat: 15 mg/kg/day, rabbit: 30 mg/kg/day). No adverse effects on pregnancy or foetal and post-natal development were detected in rats and no foetal abnormalities were observed in rabbits after oral administration of ondansetron.

A slight maternal toxicity was observed at the highest dose level in intravenous organogenesis (4.0 mg/kg/day) studies in the rabbit. Effects included maternal body weight loss and increased incidence of early foetal death. In a rat fertility study, there was a dose-related decrease in the proportion of surviving pups of the F2 generation; however, the significance of this is unclear.

Administration of ondansetron to pregnant rats and rabbits indicated there was foetal exposure to low levels of ondansetron and its metabolites. Ondansetron is retained in the foetal eye presumably bound to melanin. In rats, the transfer of ondansetron and its metabolites into breast milk was extensive. The concentration of unchanged ondansetron in breast milk was higher than in corresponding plasma samples.

Daily administration of ondansetron at dosages up to 15 mg/kg/day to pregnant rats from day 17 of pregnancy to litter day 22 had no effects on pregnancy of the parental generation or on post-natal development and mating of the F1 generation. Foetal development of the F2 generation was comparable to controls; however, the number of implantations and viable foetuses was reduced in the highest dosage group when compared with controls.

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PART III: CONSUMER INFORMATION**Pr TEVA-ONDANSETRON**

Ondansetron Tablets, USP

4 mg and 8 mg ondansetron (as ondansetron hydrochloride dihydrate)

This leaflet is part III of a three-part “Product Monograph” published when TEVA-ONDANSETRON (ondansetron hydrochloride dihydrate) was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about TEVA-ONDANSETRON. Contact your doctor or pharmacist if you have any questions about the drug.

TEVA-ONDANSETRON can only be obtained with a prescription from your doctor.

ABOUT THIS MEDICATION**What the medication is used for:**

The name of your medicine is TEVA-ONDANSETRON tablets (ondansetron hydrochloride dihydrate). This medicine is one of a group called antiemetics.

TEVA-ONDANSETRON is used for:

- the prevention of nausea (feeling of sickness) and vomiting during treatment for cancer (chemotherapy and radiotherapy),
- the prevention and treatment of nausea and vomiting after surgery.

What it does:

Treatments such as general anaesthesia, cancer chemotherapy and radiotherapy are thought to cause the release of a natural substance (serotonin), which can cause you to feel sick and to vomit. TEVA-ONDANSETRON helps to stop this from happening, thus preventing you from vomiting or feeling sick.

When it should not be used:

Do not take TEVA-ONDANSETRON if:

- you have a history of hypersensitivity (an allergic reaction) to any ingredient (see What the nonmedicinal ingredients are) in TEVA-ONDANSETRON.
- if you are taking apomorphine (used to treat Parkinson’s disease)

What the medicinal ingredient is

TEVA-ONDANSETRON tablets contain ondansetron hydrochloride dihydrate as the medicinal ingredient.

What the nonmedicinal ingredients are:

TEVA-ONDANSETRON tablets contain the following nonmedicinal ingredients: lactose monohydrate,

magnesium stearate, microcrystalline cellulose, pregelatinized starch, sodium starch glycolate, and film-coating containing: hypromellose, hydroxypropyl methylcellulose, iron oxide yellow, macrogol, polyethylene glycol, polysorbate and titanium dioxide.

What dosage form it comes in:

TEVA-ONDANSETRON tablets are supplied in two strengths, one contains 4 milligrams of ondansetron and the other contains 8 milligrams of ondansetron. Your doctor will decide which strength you need.

WARNINGS AND PRECAUTIONS

BEFORE you use TEVA-ONDANSETRON talk to your doctor or pharmacist if:

- you have a history of hypersensitivity (an allergic reaction) to any ingredient in TEVA-ONDANSETRON,
- if you have had an allergic reaction to medicines similar to TEVA-ONDANSETRON such as medicines containing *granisetron* or *palonosetron*,
- you are pregnant or likely to become pregnant,
- you are breast feeding,
- you have liver problems,
- you have signs of intestinal obstruction,
- you have a history of heart problems

If you experience wheezing and tightness of the chest, heart throbbing, swelling of eyelids, face or lips, or develop a skin rash, skin lumps or hives, **contact your doctor immediately. Do not take any more medicine unless your doctor tells you to do so.**

Serotonin Syndrome is a rare but potentially life-threatening reaction that may occur if you take TEVA-ONDANSETRON with certain other medications. It may cause serious changes in how your brain, muscles and digestive system work. Be sure to tell your healthcare professional all the medicines you are taking.

INTERACTIONS WITH THIS MEDICATION

As with most medicines, interactions with other drugs are possible. To avoid potentially life-threatening reactions tell your healthcare professional about **ALL** the medications you take, including those prescribed by other doctors, vitamins, minerals, natural supplements or alternative medicines. It is important that your doctor know about all your medication so that you get the best possible treatment. Tell your doctor if you are taking carbamazepine, phenytoin, or rifampicin. If you are taking any medicines containing tramadol, TEVA-ONDANSETRON may decrease its effectiveness.

Also, make sure you tell your doctor or pharmacist if you are taking:

- Drugs used to treat heart rhythm disorders
- Other drugs that may disturb heart rhythm
- Antipsychotics
- Antidepressants
- Antibiotics or antifungals
- Opioid analgesics (painkillers)
- Other drugs to treat nausea and vomiting
- Asthma drugs
- Cancer drugs
- Diuretics
- Other drugs that affect serotonin including SSRI*s, SNRI**s, triptans, MAOIs*** (including the antibiotic linezolid and methylene blue), drugs that contain tryptophan, or St. John’s Wort.

*SSRI (Selective Serotonin-Reuptake Inhibitors) – used to treat depression or anxiety, e.g. escitalopram, citalopram, fluoxetine, paroxetine, sertraline.

**SNRI (Serotonin Noradrenalin Reuptake Inhibitors) – used to treat depression or anxiety, e.g. duloxetine, venlafaxine, desvenlafaxine.

***MAOIs (Monoamine Oxidase Inhibitors) – used to treat depression, Parkinson’s disease, e.g., phenelzine, rasagiline, selegiline.

PROPER USE OF THIS MEDICATION

The label on the container of your medicine should tell you how often to take your medicine and how many doses you should take each time. If not, or if you are not sure, consult your doctor or pharmacist.

Do not take more doses, or take them more often than your doctor prescribes. If, however, you vomit within one hour of taking your medicine, you should take the same amount of medicine again. If vomiting persists, consult your doctor.

Usual dose:

Chemotherapy Induced Nausea and Vomiting

Based on how likely you are to experience nausea and/or vomiting, caused by your cancer treatment, your doctor will tell you the amount you need to take and how frequently.

Adult: You may receive TEVA-ONDANSETRON before and/or after chemotherapy. The dose of TEVA-ONDANSETRON is between 8 and 24 mg a day (taken orally) for up to 5 days depending on the potential of your chemotherapy treatment to cause you to vomit and/or have nausea.

Children (4 to 12 years): After chemotherapy, take 4 mg orally every 8 hours for up to 5 days.

Radiotherapy Induced Nausea and Vomiting

Adult: Take 8 mg orally 1 to 2 hours before radiotherapy. After therapy, take 8 mg orally every 8 hours for up to 5 days after a course of treatment.

Prevention of Post-Operative Nausea and Vomiting

Adult: Take 16 mg orally one hour before anaesthesia.

If you have a liver problem, your dose may be altered. Please follow the instructions of your doctor.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose and do not feel sick, take the next dose when it is due.

If you forget to take your medicine and feel sick or vomit, take a dose as soon as possible.

If your doctor decides to stop the treatment, do not keep any leftover medicine unless your doctor tells you to.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

You may experience headaches, a feeling of warmth, flushing or constipation, while taking TEVA-ONDANSETRON. Although uncommon, low blood pressure and hiccups have also been reported.

There is no need to stop taking your medicine, but you should tell your doctor about these symptoms at your next visit.

If your nausea (feeling of sickness) or vomiting do not improve while taking TEVA-ONDANSETRON, consult your doctor for further advice.

If you feel unwell or have any symptoms that you do not understand, you should contact your doctor immediately.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Side Effect/ Symptom	Talk with your Doctor or Pharmacist	Stop taking drug and seek immediate emergency assistance
Uncommon		

Side Effect/ Symptom	Talk with your Doctor or Pharmacist	Stop taking drug and seek immediate emergency assistance
Heart problems such as fast/slow heartbeat, chest pain		√
Seizures		√
Upward rolling of the eyes, abnormal muscular stiffness/ body movements/ shaking		√
Rare		
Eye problems such as blurred vision	√	
Immediate allergic reaction and symptoms such as swelling of the mouth, throat, difficulty in breathing, rash, hives, increased heart rate		√
Disturbance in heart rhythm (dizziness, palpitations, fainting)		√
Serotonin Syndrome: Symptoms of Serotonin Syndrome have been observed while taking ondansetron hydrochloride with certain other medications. Symptoms include: <ul style="list-style-type: none"> • agitation, confusion, restlessness, hallucinations, mood changes, unconsciousness, coma • fast heartbeat, changes in blood pressure • muscle shakes, jerks, twitches or 		√

Side Effect/ Symptom	Talk with your Doctor or Pharmacist	Stop taking drug and seek immediate emergency assistance
stiffness, overactive reflexes, loss of coordination <ul style="list-style-type: none"> • nausea, vomiting, diarrhea, fever, sweating, shivering 		
Very Rare		
Eye problems such as temporary blindness	√	
Signs of serious skin reactions (skin rash, redness of the skin, blistering of the lips, eyes or mouth, and skin peeling)		√

This is not a complete list of side effects. For any unexpected effects while taking TEVA-ONDANSETRON, contact your doctor or pharmacist.

HOW TO STORE IT

Keep your medicine in a safe place where children cannot reach it. Your medicine may harm them.

TEVA-ONDANSETRON tablets should be stored between 15°C and 30°C.

Last revised: January 22, 2016

REPORTING SUSPECTED SIDE EFFECTS

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at MedEffect (<http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php>);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
 - Fax to 1-866-678-6789 (toll-free), or
 - Mail to: Canada Vigilance Program
Health Canada, Postal Locator 0701E
Ottawa, ON
K1A 0K9
Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (<http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php>).

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

Remember: This medicine is for you. Only a doctor can prescribe it for you. Never give it to someone else. It may harm them even if their symptoms are the same as yours.

This leaflet does not contain the complete information about your medicine. If any questions remain unanswered or you are not sure about something, you should ask your doctor or pharmacist.

You may want to read this leaflet again. **Please Do Not Throw It Away** until you have finished your medicine.

This document plus the full product monograph, prepared for health professionals can be found by contacting Teva Canada Limited at:

1-800-268-4127 ext. 1255005 (English)

1-877-777-9117 (French)

or druginfo@tevacanada.com

This leaflet was prepared by:

Teva Canada Limited

30 Novopharm Court

Toronto, Ontario

Canada, M1B 2K9

PART III: CONSUMER INFORMATION**PrONDANSETRON INJECTION**

Ondansetron Injection, USP

2 mg/mL ondansetron (equivalent to ondansetron hydrochloride dehydrate)

This leaflet is part III of a three-part “Product Monograph” published when ONDANSETRON INJECTION (ondansetron hydrochloride dihydrate) was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about ONDANSETRON INJECTION. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION**What the medication is used for:**

The name of your medicine is ONDANSETRON INJECTION (ondansetron hydrochloride dihydrate). This medicine is one of a group called antiemetics.

ONDANSETRON INJECTION is used for:

- the prevention of nausea (feeling of sickness) and vomiting during treatment for cancer (chemotherapy).
- the prevention and treatment of nausea and vomiting after surgery.

What it does:

Treatments such as general anaesthesia and cancer chemotherapy are thought to cause the release of a natural substance (serotonin), which can cause you to feel sick and to vomit. ONDANSETRON INJECTION helps to stop this from happening, thus preventing you from vomiting or feeling sick.

When it should not be used:

Do not take ONDANSETRON INJECTION if:

- you have a history of hypersensitivity (an allergic reaction) to any ingredients (see What the nonmedicinal ingredients are below) in ONDANSETRON INJECTION.
- if you are taking apomorphine (used to treat Parkinson’s disease).

What the medicinal ingredient is:

ONDANSETRON INJECTION contains ondansetron (as ondansetron hydrochloride dihydrate) as the medicinal ingredient.

What the nonmedicinal ingredients are:

ONDANSETRON INJECTION (Preservative-Free, 2 mL and 4 mL vials) contains the following non-medicinal

ingredients: citric acid monohydrate, sodium chloride, sodium citrate dihydrate and Water for Injection.

ONDANSETRON INJECTION (Preservative, 20 mL vial) contains the following non-medicinal ingredients: citric acid monohydrate, methylparaben, propylparaben, sodium chloride, sodium citrate dihydrate, and Water for Injection

What dosage forms it comes in:

ONDANSETRON INJECTION is available as ondansetron 2 mg/mL (as hydrochloride dihydrate) for intravenous use.

WARNINGS AND PRECAUTIONS

BEFORE you use ONDANSETRON INJECTION talk to your doctor or pharmacist if:

- you have a history of hypersensitivity (an allergic reaction) to any ingredient in ONDANSETRON INJECTION,
- if you have had an allergic reaction to medicines similar to ONDANSETRON INJECTION such as medicines containing *granisetron* or *palonosetron*,
- you are pregnant or likely to become pregnant,
- you are breast feeding,
- you have liver problems,
- you have signs of intestinal obstruction,
- you have a history of heart problems,
- you have QT/QTc prolongation or a family history of QT/QTc prolongation,
- you have low blood levels of potassium, magnesium, or calcium.

If you experience wheezing and tightness of the chest, heart throbbing, swelling of eyelids, face or lips, or develop a skin rash, skin lumps or hives, **tell your doctor immediately.**

When given intravenously, ondansetron hydrochloride has an effect on the electrical activity of the heart known as QT/QTc prolongation. This effect can be measured as a change in the electrocardiogram (ECG). In very rare cases, drugs with this effect on the ECG can lead to disturbances in heart rhythm (arrhythmias/dysrhythmias) that could result in dizziness, palpitations (sensation of rapid, pounding, or irregular heart beat), fainting or death. These heart rhythm disturbances are more likely in patients with risk factors, such as heart disease, or in the presence of certain interacting drugs. In general, females and people more than 65 years in age are at higher risk. It is important to follow the instructions of your doctor with regard to dosing or any special tests. If you experience any symptoms of a possible heart rhythm disturbance, such as dizziness, palpitations (sensation of rapid, pounding, or irregular heart beat), or fainting, you should seek immediate medical attention.

Serotonin Syndrome is a rare but potentially life-threatening reaction that may occur if you take ONDANSETRON INJECTION with certain other medications. It may cause serious changes in how your brain, muscles and digestive system work. Be sure to tell your healthcare professional all the medicines you are taking.

INTERACTIONS WITH THIS MEDICATION

As with most medicines, interactions with other drugs are possible. To avoid potentially life-threatening reactions tell your healthcare professional about **ALL** the medications you take, including those prescribed by other doctors, vitamins, minerals, natural supplements or alternative medicines. It is important that your doctor know about all your medication so that you get the best possible treatment. Tell your doctor if you are taking carbamazepine, phenytoin or rifampicin. If you are taking any medicines containing tramadol, ONDANSETRON INJECTION may decrease its effectiveness.

Also, make sure you tell your doctor or pharmacist if you are taking:

- Drugs used to treat heart rhythm disorders
- Other drugs that may disturb heart rhythm
- Antipsychotics
- Antidepressants
- Antibiotics or antifungals
- Opioid analgesics (painkillers)
- Other drugs to treat nausea and vomiting
- Asthma drugs
- Cancer drugs
- Diuretics
- Other drugs that affect serotonin including SSRI*s, SNRI**s, triptans, MAOIs*** (including the antibiotic linezolid and methylene blue), drugs that contain tryptophan, or St. John’s Wort.

*SSRI (Selective Serotonin-Reuptake Inhibitors) – used to treat depression or anxiety, e.g. escitalopram, citalopram, fluoxetine, paroxetine, sertraline.

**SNRI (Serotonin Noradrenalin Reuptake Inhibitors) – used to treat depression or anxiety, e.g. duloxetine, venlafaxine, desvenlafaxine.

***MAOIs (Monoamine Oxidase Inhibitors) – used to treat depression, Parkinson’s disease, e.g., phenelzine, rasagiline, selegiline.

PROPER USE OF THIS MEDICATION

ONDANSETRON INJECTION is not self administered by individual. It should be administered under the supervision of a health professional.

Usual dose:

Chemotherapy Induced Nausea and Vomiting

You will receive ONDANSETRON INJECTION by intravenous infusion. Based on how likely you are to experience nausea and/or vomiting, caused by your cancer treatment, your doctor will determine the appropriate dose regimen for you.

Adult: The single IV dose of ONDANSETRON INJECTION is between 8 and 16 mg before your chemotherapy. You may also receive TEVA-ONDANSETRON to be taken orally after your chemotherapy.

Children (4 to 12 years): The dose is 3 to 5 mg/m² just before chemotherapy.

Post-Operative Nausea and Vomiting

Adult: For prevention of post-operative nausea and vomiting, the dose is 4 mg at the time of surgery. For treating postoperative nausea and vomiting, the dose is 4 mg after surgery. If you have a liver problem, your dose may be altered.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

You may experience headaches, a feeling of warmth, flushing or constipation, while taking ONDANSETRON INJECTION. You may also experience pain, redness and burning sensation at the injection site.

Although uncommon, low blood pressure and hiccups have also been reported.

If your nausea (feeling of sickness) or vomiting do not improve while taking ONDANSETRON INJECTION, consult your doctor for further advice.

If you feel unwell or have any symptoms that you do not understand, tell your doctor immediately.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Side Effect/ Symptom	Talk with your Doctor Immediately
Uncommon	
Heart problems such as fast/slow heart beat, chest pain	√

Side Effect/ Symptom	Talk with your Doctor Immediately
Seizures	√
Upward rolling of the eyes, abnormal muscular stiffness/body movements/shaking	√
Rare	
Eye problems such as blurred vision	√
Immediate allergic reaction and symptoms such as swelling of the mouth, throat, difficulty in breathing, rash, hives, increased heart rate	√
Disturbance in heart rhythm (dizziness, palpitations, fainting)	√
Serotonin Syndrome: Symptoms of Serotonin Syndrome have been observed while taking ondansetron with certain other medications. Symptoms include:	√
<ul style="list-style-type: none"> • agitation, confusion, restlessness, hallucinations, mood changes, unconsciousness, coma • fast heartbeat, changes in blood pressure • muscle shakes, jerks, twitches or stiffness, overactive reflexes, loss of coordination • nausea, vomiting, diarrhea, fever, sweating, shivering 	
Very Rare	
Eye problems such as temporary blindness	√
Signs of serious skin reactions (skin rash, redness of the skin, blistering of the lips, eyes or mouth, and skin peeling)	√

This is not a complete list of side effects. For any unexpected effects while taking ONDANSETRON INJECTION, contact your doctor.

HOW TO STORE IT

ONDANSETRON INJECTION should be stored between 15°C and 30°C.

ONDANSETRON INJECTION should not be frozen and should be protected from light. ONDANSETRON INJECTION must not be autoclaved.

Intravenous solutions should be prepared at the time of infusion. ONDANSETRON INJECTION, preservative-free and preservative, when diluted with the recommended intravenous solutions, should be used within 24 hours if stored at room temperature or used within 72 hours if stored in a refrigerator, due to possible microbial contamination during preparation.

REPORTING SUSPECTED SIDE EFFECTS

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at MedEffect (<http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php>);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
 - Fax to 1-866-678-6789 (toll-free), or
 - Mail to: Canada Vigilance Program
Health Canada, Postal Locator 0701E
Ottawa, ON
K1A 0K9
Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (<http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php>).

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

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This leaflet was prepared by:
Teva Canada Limited
30 Novopharm Court
Toronto, Ontario
Canada, M1B 2K9

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