PRODUCT MONOGRAPH

# [Pr]ONDANSETRON INJECTION USP

2 mg/mL Ondansetron
(as ondansetron hydrochloride dihydrate)

Sterile
Antiemetic

(5-$HT_3$ receptor antagonist)

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**(as ondansetron hydrochloride dihydrate)**

## PART I: HEALTH PROFESSIONAL INFORMATION

### SUMMARY PRODUCT INFORMATION

| Route of Administration | Dosage Form / Strength | All Nonmedicinal Ingredients |
|---|---|---|
| Intravenous | Injection/<br><br>2 mg/mL ondansetron (as ondansetron hydrochloride dihydrate) | Citric acid monohydrate, sodium citrate dihydrate, sodium chloride, water.<br><br>Multidose vials also contain the preservative agents methylparaben and propylparaben. |

### INDICATIONS AND CLINICAL USE

**Adults**
Ondansetron Injection USP (ondansetron hydrochloride dihydrate) is indicated for:

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

- the prevention and treatment of post-operative nausea and vomiting.

**Pediatrics (4 to 18 years of age)**

**Post-Chemotherapy Induced Nausea and Vomiting**
Ondansetron hydrochloride was effective and well tolerated when given to children 4 to 12 years of age (see **DOSAGE AND ADMINISTRATION**). Ondansetron Injection USP is not indicated for the treatment of children 3 years of age or younger.

**Post-Operative Nausea and Vomiting**
Ondansetron Injection USP is not indicated for use in any age group of this population.

**Geriatrics (> 65 years of age)**

**Post-Chemotherapy Induced Nausea and Vomiting**
Efficacy and tolerance of ondansetron 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

- Ondansetron Injection USP (ondansetron hydrochloride) is contraindicated in patients with a history of hypersensitivity to the drug or any components of its formulation. For a complete listing, see **DOSAGE FORMS, COMPOSITION AND PACKAGING.**
- 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-$HT_3$ antagonists. Patients who have experienced hypersensitivity reactions to one 5-$HT_3$ antagonist have experienced more severe reactions upon being challenged with another drug of the same class. The use of a different 5-$HT_3$ 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-$HT_3$ 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.

Ondansetron Injection USP (ondansetron hydrochloride dihydrate) is not effective in preventing motion-induced nausea and vomiting.

**Neurologic**

**Serotonin syndrome/Neuroleptic Malignant Syndrome-like events:** Cases of life-threatening serotonin syndrome or neuroleptic malignant syndrome-like events have been reported with 5-$HT_3$ receptor antagonist antiemetics, including ondansetron, 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 Injection USP 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 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 $P_{450}$ drug-metabolizing enzyme system of the liver. Because ondansetron is metabolised by hepatic cytochrome $P_{450}$ 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 and ondansetron have been administered to over 2500 patients worldwide in controlled clinical trials and have 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 to 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 have been supplied since the launch of the product worldwide. The following events have been spontaneously reported during post-approval use of ondansetron, 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 intravenous (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-$HT_3$ receptor antagonist antiemetics, including ondansetron, 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 $P_{450}$ 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 Injection USP 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 1C 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 Injection USP 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-$HT_3$ 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 nonselective MAOI), and methylene blue; See **WARNINGS AND PRECAUTIONS, Neurologic**)

## DOSAGE AND ADMINISTRATION

### Dosing Considerations

Ondansetron Injection USP has a dose dependent QTc prolongation effect. For intravenous (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 favored.

### 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 USP (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 USP 8 mg infused intravenously over 15 minutes given at least 30 minutes prior to chemotherapy. A maximum initial dose of Ondansetron Injection USP 16 mg intravenously infused over 15 minutes may be used. A single intravenous 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 USP intravenous 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: Cardiovascular, QTc Interval Prolongation; DRUG INTERACTIONS: Drug-Drug Interactions, QTc-Prolonging Drugs; ACTIONS AND CLINICAL PHARMACOLOGY: Electrocardiography**).

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

The efficacy of Ondansetron Injection USP in highly emetogenic chemotherapy may be enhanced by the addition of a single intravenous dose of dexamethasone sodium phosphate 20 mg administered prior to chemotherapy.

*Post-chemotherapy:*

Two additional doses of Ondansetron Injection USP 8 mg intravenous (15 minutes infusions) may be given 4 and 8 hours after the initial dose of Ondansetron Injection USP.

After the first 24 hours, ondansetron hydrochloride 8 mg may be taken orally every 8 hours[1] for up to 5 days. ***Please consult the Product Monograph of ondansetron hydrochloride tablets and/or oral solution for further information.***

**Note: Ondansetron Injection USP is only available in the 2 mg/mL intravenous dosage form.**

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

*Initial Dose:*

Ondansetron Injection USP 8 mg infused intravenously over 15 minutes, given at least 30 minutes prior to chemotherapy; or ondansetron hydrochloride 8 mg orally 1 to 2 hours prior to chemotherapy. ***Please consult the Product Monograph of ondansetron hydrochloride tablets and/or oral solution for further information.***

**Note: Ondansetron Injection USP is only available in the 2 mg/mL intravenous dosage form.**

*Post-chemotherapy:*

Ondansetron hydrochloride 8 mg orally twice daily for up to 5 days. ***Please consult the Product Monograph of ondansetron hydrochloride tablets and/or oral solution for further information.***

**Note: Ondansetron Injection USP is only available in the 2 mg/mL intravenous dosage form.**

***Use in Children:***

Clinical experience of ondansetron for the treatment of Post-Chemotherapy Induced Nausea and Vomiting in children is currently limited, however, ondansetron was effective and well tolerated when given to children 4-12 years of age. Ondansetron Injection USP should be given intravenously at a dose of 3-5 mg/m$^2$ over 15 minutes at least 30 minutes before chemotherapy. After therapy, ondansetron 4 mg should be given orally every 8[2] hours for up to 5 days. ***Please consult the Product Monograph of ondansetron hydrochloride tablets and/or oral solution for further information.*** For children 3 years of age and younger, there is insufficient information available to make dosage recommendations, therefore, Ondansetron Injection USP is not indicated for the treatment of children 3 years of age or younger (see **INDICATIONS AND CLINICAL USE**).

[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 daily dosage regimens for other patient groups should be based on an assessment of the needs and responsiveness of the individual patient.

[2] 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.

**Note: Ondansetron Injection USP is only available in the 2 mg/mL intravenous dosage form.**

***Use in Elderly:***
In patients 65 years of age or older, all intravenous 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 intravenous dose of Ondansetron Injection USP 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 USP 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 predicated increase of the risk for a slight QTcF interval prolongation above 10 ms (from baseline) for about 10 min. ECG monitoring may be considered.

**Post-operative Nausea and Vomiting**

***Use in Adults:***

For prevention of post-operative nausea and vomiting Ondansetron Injection USP may be administered as a single dose of 16 mg given orally one hour prior to anaesthesia. ***Please consult the Product Monograph of ondansetron hydrochloride tablets and/or oral solution for further information.***

**Note: Ondansetron Injection USP is only available in the 2 mg/mL intravenous dosage form.**

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 in the prevention and treatment of post-operative nausea and vomiting in children. Ondansetron injection USP is not indicated for this use in children (see **INDICATIONS AND CLINICAL USE**).

***Use in Elderly:***

There is limited experience in the use of ondansetron in the prevention and treatment of post-operative nausea and vomiting in the elderly. Ondansetron injection USP is 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 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. ***Please consult the Product Monograph of ondansetron hydrochloride tablets and/or oral solution for further information.***

**Note: Ondansetron Injection USP is only available in the 2 mg/mL intravenous dosage form.**

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 USP should only be mixed with the infusion solutions recommended below:

For Single and Multi-Dose Vials
5% w/v Dextrose Injection
0.9% w/v Sodium Chloride Injection

**NOTE:** As with all parenteral drug products, injections/intravenous ad-mixtures 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.

**OVERDOSAGE**

For management of a suspected drug overdose contact your regional Poison Control Centre.

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 overdosage, 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 overdosage 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.

## ACTION AND CLINICAL PHARMACOLOGY

### Mechanism of Action

Ondansetron is a selective antagonist of the serotonin receptor subtype, 5-$HT_3$. 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-$HT_3$ 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-$HT_3$ 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

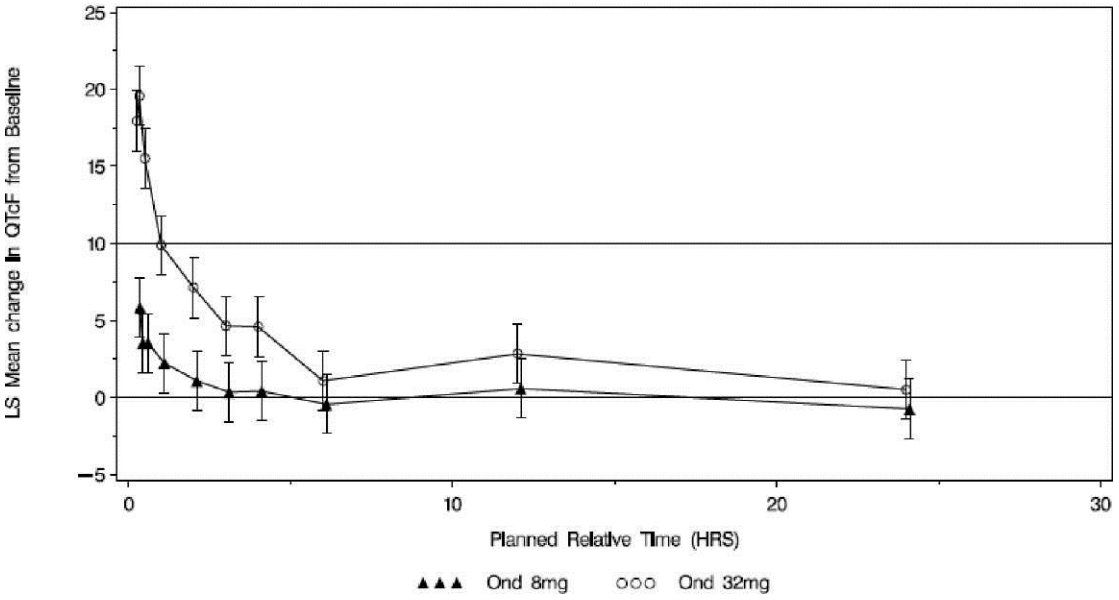
*In vitro* metabolism studies have shown that ondansetron is a substrate for human hepatic cytochrome $P_{450}$ enzymes, including CYP1A2, CYP2D6 and CYP3A4. In terms of overall ondansetron turnover, CYP3A4 played the predominant role. Because of the multiplicity of metabolic enzymes capable of metabolising 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. On the basis of pharmacokinetic-pharmacodynamic modelling, an 8 mg oral dose of ondansetron 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/m$^2$ 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 to 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%.

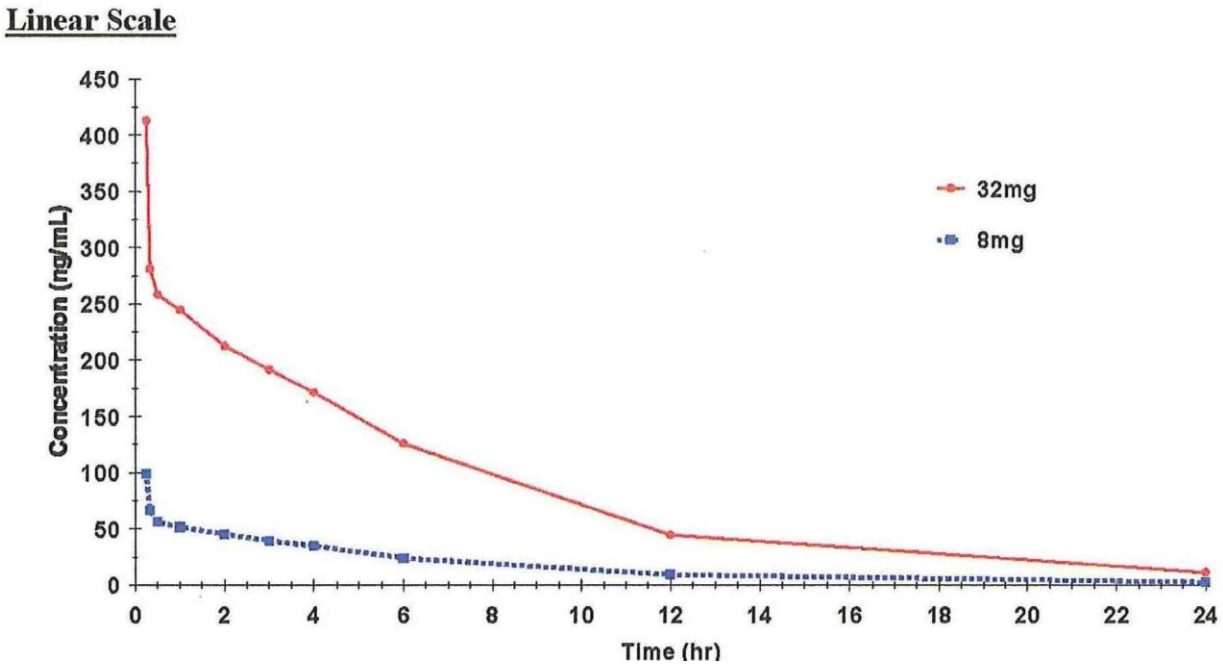
Following oral or intravenous administration, ondansetron is extensively metabolised and excreted in the urine and faeces. In humans, less than 10% of the dose is excreted unchanged in

the urine. The major urinary metabolites are glucuronide conjugates (45%), sulphate conjugates (20%) and hydroxylation products (10%).

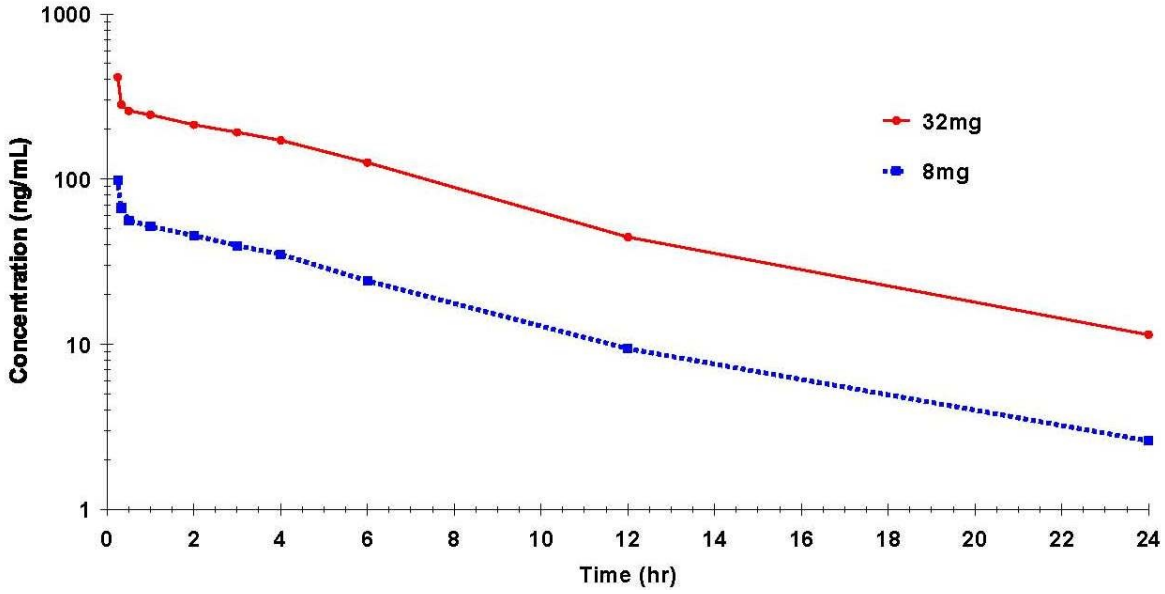
The half-life of ondansetron after either an 8 mg oral dose or intravenous dose was approximately 3 to 4 hours and may be extended to 6 to 8 hours in the elderly.

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 Intravenous Doses**



**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. For intravenous dosing, specific information is provided for patients over 65 years of age and over 75 years of age (see **DOSAGE AND ADMINISTRATION:** ***Use in Elderly***).

## STORAGE AND STABILITY

Ondansetron Injection USP (ondansetron hydrochloride dihydrate) should be stored between 2 and 25°C. Ondansetron Injection USP should not be frozen and should be protected from light. Ondansetron Injection USP must not be autoclaved.

Unused portions of the 2 mL and 4 mL single dose formats should be discarded and the contents of the 20 mL multi-dose format 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 USP in vials, 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.

## DOSAGE FORMS, COMPOSITION AND PACKAGING

Ondansetron Injection USP:
Ondansetron 2 mg/mL (as ondansetron hydrochloride dihydrate) for intravenous use is supplied in single dose vials of 2 mL (4 mg) and 4 mL (8 mg) vials, in boxes of 5 vials and in multi-dose vials of 20 mL (40 mg), packed in individual cartons.

**Composition**

Ondansetron Injection USP (vials) contains 2 mg/mL of ondansetron base, in the form of ondansetron hydrochloride dihydrate.

Ondansetron Injection USP (preservative-free, 2 mL and 4 mL single dose vials) also contains:

| | |
|---|---|
| citric acid monohydrate | 0.50 mg/mL |
| sodium citrate dihydrate | 0.25 mg/mL |
| sodium chloride | 9.00 mg/mL |
| water | qs |

Ondansetron Injection USP (with preservatives, 20 mL multi dose vial) also contains:

| | |
|---|---|
| citric acid monohydrate | 0.50 mg/mL |
| sodium citrate dihydrate | 0.25 mg/mL |
| sodium chloride | 8.3 mg/mL |
| methylparaben (preservative agent) | 1.2 mg/mL |
| propylparaben (preservative agent) | 0.15 mg/mL |
| water | qs |

# PART II: SCIENTIFIC INFORMATION

## PHARMACEUTICAL INFORMATION

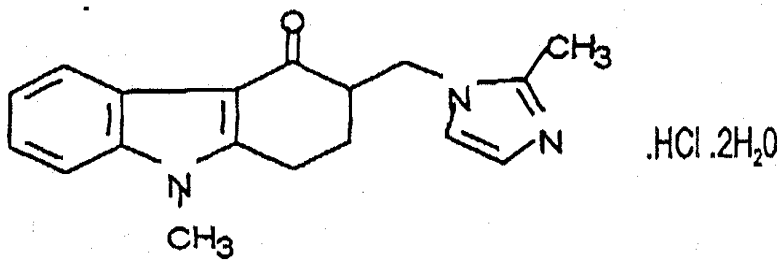
### Drug Substance

Proper name: ondansetron hydrochloride dihydrate

Chemical name: 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one, hydrochloride, dihydrate

Molecular formula and molecular mass: $C_{18}H_{19}N_3O \cdot HCl \cdot 2H_2O$
365.9 g/mol

Structural formula:




Physicochemical properties:

**Description and Solubility***:*

Ondansetron hydrochloride dihydrate is a white to off-white powder. It is soluble at room temperature in either water (−32 mg/mL) or normal saline (−8 mg/mL) forming a clear and colourless solution. The melting point of ondansetron hydrochloride dihydrate is about 177°C. pKa is 7.4 and pH of 1% w/v solution in water is approximately 4.6. The distribution coefficient between n-octanol and water is pH dependent:
log D = 2.2 at a pH of 10.60
log D = 0.6 at a pH of 5.95

## CLINICAL TRIALS

### 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[ι] 3 doses of 0.15 mg/kg** | **Placebo[ι] 3 doses of placebo** | **Ondansetron 8 mg IV + 1 mg/hr, 24 hours** | **Ondansetron 8 mg IV** | **Ondansetron 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%) | - | - | - |

[ι] Results are from an initial study using a different dosing regimen.

| PREVENTION OF POST-OPERATIVE EMESIS - RESPONSE OVER 24 HOURS[χ] | | | | | | |
|---|---|---|---|---|---|---|
| | **ORAL PREVENTION** | | | **INTRAVENOUS PREVENTION** | | |
| **DOSE** | **Ondansetron 16 mg od** | **Placebo** | **p Value** | **Ondansetron 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 |

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

| TREATMENT OF POST-OPERATIVE EMESIS - RESPONSE OVER 24 HOURS$\chi$ | | | |
|---|---|---|---|
| | INTRAVENOUS TREATMENT | | |
| **DOSE** | **Ondansetron 4 mg IV** | **Placebo** | **p Value** |
| **# of patients** | 104 | 117 | |
| **Treatment Response** 0 emetic episodes | 49 (47%) | 19 (16%) | <0.001 |

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

## 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 to 10 mg/kg), cyclophosphamide (200 mg/kg) or irradiation (2 and 8 Gy, 250 kV). Intravenous doses of ondansetron (0.1 to 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.

The antiemetic effects of ondansetron (0.1 mg/kg) in combination with dexamethasone (2 to 5 mg/kg) were potentiated in ferrets with cyclosphosphamide-induced emesis, compared with ondansetron alone. Ondansetron with dexamethasone produced a significant reduction in retching (65%) and vomiting (72%).

Serotonin receptors of the 5-$HT_3$ 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-$HT_3$ antagonists directly into the area postrema eliminate cisplatin-induced emesis, while 5-$HT_1$-like (methiothepin maleate) and 5-$HT_2$ (ketanserin) antagonists have no effect.

Ondansetron is highly selective for 5-$HT_3$ receptors and shows negligible binding to other receptors such as 5-$HT_1$-like, 5-$HT_2$, α1 and α2 adrenoceptors, β1 and β2 adrenoceptors, $D_1$ and $D_2$ muscarinic, nicotinic, $GABA_A$, $H_1$ and $H_2$ 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 $D_2$ 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 to 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 intravenous 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 to 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 $LD_{50}$ 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<br>Dog | 18 months<br>12 months | 1<br>12 | Usually transient and restricted to highest dose |

***Carcinogenicity Studies:***

| Species | Route | Dose (mg/kg/day) | Duration of Study | Results |
|---|---|---|---|---|
| Mice | Oral | 1-40<br>(max. oral dose 30) | 2 years | No treatment related increases in tumour incidence. |
| Rats | Oral | 1-25<br>(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 fetal and post-natal development were detected in rats and no fetal 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 fetal 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 fetal exposure to low levels of ondansetron and its metabolites. Ondansetron is retained in the fetal 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. Fetal development of the F2 generation was comparable to controls; however, the number of implantations and viable fetuses was reduced in the highest dosage group when compared with controls.

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**PART III: CONSUMER INFORMATION**

**[Pr]Ondasetron Injection USP**
**2 mg/mL Ondansetron**
**(as ondansetron hydrochloride dihydrate)**

**This leaflet is part III of a three-part "Product Monograph" published when Ondansetron Injection USP (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 USP (ondansetron hydrochloride dihydrate). 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 USP. This medicine is one of a group called antiemetics.

Ondansetron Injection USP 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 USP 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 USP if:

- you have a history of hypersensitivity (an allergic reaction) to any ingredient (see What the medicinal ingredient and nonmedicinal ingredients are) in Ondansetron Injection USP.
- if you are taking apomorphine (used to treat Parkinson's disease).

**What the medicinal ingredient is:**
Ondansetron Injection USP contains ondansetron hydrochloride dihydrate as the medicinal ingredient.

**What the nonmedicinal ingredients are:**
Ondansetron Injection USP contains the following non-medicinal ingredients: citric acid monohydrate, sodium citrate dihydrate, sodium chloride and water. The multidose vials also contain methylparaben and propylparaben as preservative agents.

**What dosage forms it comes in:**
Ondansetron 2 mg/mL (as hydrochloride dihydrate) for intravenous use is supplied in single dose vials of 2 mL (4 mg) and 4 mL (8 mg) vials, in boxes of 5 vials and in multi-dose vials of 20 mL (40 mg), packed in individual cartons.

## WARNINGS AND PRECAUTIONS

BEFORE you use Ondansetron Injection USP talk to your doctor or pharmacist if:

- you have a history of hypersensitivity (an allergic reaction) to any ingredient in Ondansetron Injection USP.
- If you have had an allergic reaction to medicines similar to 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.
- 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, **contact your doctor immediately.**

When given intravenously, ondansetron 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 USP 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 USP 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 USP is not self administered by individuals. It should be administered under the supervision of a health professional.

**Usual dose**

**Chemotherapy Induced Nausea and Vomiting:**
You will receive Ondansetron Injection USP 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 intravenous dose of Ondansetron Injection USP is between 8 and 16 mg before your chemotherapy. You may also receive ondansetron to be taken orally after your chemotherapy.

**Children (4 to 12 years):** The dose is 3 to 5 mg/m$^2$ 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 post-operative nausea and vomiting, the dose is 4 mg after surgery. If you have a liver problem, your dose may be altered.

## SIDE EFFECTS AND WHAT TO DO ABOUT THEM

You may experience headaches, a feeling of warmness, flushing or constipation, while taking Ondansetron Injection USP. 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 USP, 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

| Frequency | Side Effect / Symptom | Talk with your Doctor immediately |
|---|---|---|
| Uncommon | Heart problems such as fast/slow heart beat, chest pain | X |
| | Seizures | X |
| | Upward rolling of the eyes, abnormal muscular stiffness/body movements/shaking | X |
| Rare | Eye problems such as blurred vision | X |
| | Immediate allergic reaction and symptoms such as swelling of the mouth, throat, difficulty in breathing, rash, hives, increased heart rate | X |
| | Disturbance in heart rhythm (dizziness, palpitations, fainting) | X |
| | Serotonin Syndrome:<br>Symptoms of Serotonin Syndrome have been observed while taking Ondansetron Injection USP with certain other medications. Symptoms include:<br>•agitation, confusion, restlessness, hallucinations, mood changes, unconsciousness, coma.<br>•fast heartbeat, changes in blood pressure<br>• Muscle shakes, jerks, twitches or stiffness, overactive reflexes, loss of coordination<br>• nausea, vomiting, diarrhea, fever, | X |

| SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM | | |
|---|---|---|
| **Frequency** | **Side Effect / Symptom** | **Talk with your Doctor immediately** |
| | sweating, shivering. | |
| Very Rare | Eye problems such as temporary blindness | X |
| | Signs of serious skin reactions (skin rash, redness of the skin, blistering of the lips, eyes or mouth, and skin peeling.) | X |

*This is not a complete list of side effects. For any unexpected effects while taking Ondansetron Injection USP, contact your doctor.*

## HOW TO STORE IT

Ondansetron Injection USP should be stored between 2 and 25 °C. Ondansetron Injection USP should not be frozen and should be protected from light.

**Reporting 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;
• 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, Ontario
  K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect.

*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

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.

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, Hospira Healthcare Corporation at: 1-866-488-6088

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