PRODUCT MONOGRAPH

^{Pr}ONDANSETRON INJECTION USP

2 mg/mL ondansetron (supplied as ondansetron hydrochloride dihydrate)

Sterile solution

For intravenous infusion only

Antiemetic

(5-HT_3 receptor antagonist)

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[Pr]ONDANSETRON INJECTION USP
Ondansetron (supplied as ondansetron hydrochloride dihydrate)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Intravenous	Injection / 2 mg/mL ondansetron (as hydrochloride dihydrate)	2 mL or 4 mL ampoule: 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
Ondansetron Injection USP (ondansetron hydrochloride dihydrate) 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 (< 18 years of age)

Post-Chemotherapy
Clinical experience of ondansetron in children is currently limited, however, ondansetron was effective and well tolerated when given to children 4-12 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-Radiotherapy
Safety and efficacy of ondansetron in any age group in this population following radiotherapy has not been established and is therefore not indicated for use in this population.

Post-Operative Nausea and Vomiting
Safety and efficacy of ondansetron in any age group in this population for the prevention and treatment of post-operative nausea and vomiting has not been established and is not indicated for use in this group.

Geriatrics (> 65 years of age)

Post-Chemotherapy and Radiotherapy
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 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 dihydrate) is 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

General
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.

Rarely, transient ECG changes including QT interval prolongation have been reported in patients receiving ondansetron. In addition, post-marketing cases of Torsade de Pointes have been reported in patients using ondansetron (see Post-Market Adverse Drug Reactions). Avoid use of ondansetron in patients with congenital long QT syndrome and in patients who may develop prolongation of QTc, including patients with electrolyte abnormalities and patients taking other medicinal products that lead to QT prolongation, unless the nausea and vomiting cannot be controlled by other drugs.

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

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

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.

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 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.

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.

Special Senses:
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.

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.

General Disorders:
Rare cases of hypersensitivity reactions, such as, 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 (including Torsade de Pointes) have been reported (see WARNINGS AND PRECAUTIONS).

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 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.

Respiratory, Thoracic and Mediastinal Disorders:
There have also been rare reports of hiccups.

Very rare reports have been received for bullous skin and mucosal reactions (including Stevens-Johnson syndrome and toxic epidermal necrolysis). These reports have occurred in patients taking other medications that can be associated with bullous skin and mucosal reactions.

DRUG INTERACTIONS

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

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).

DOSAGE AND ADMINISTRATION

Dosing Considerations

Chemotherapy Induced Nausea and Vomiting:

Ondansetron 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 route of administration and dose of ondansetron should be flexible in the range of 8-32 mg a day. The selection of dose regimen should be determined by the severity of the emetogenic challenge (See Recommended Dose and Dosage Adjustment).

Recommended Dose And Dosage Adjustment

Chemotherapy Induced Nausea And Vomiting:

Use in Adults:

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

Ondansetron has been shown to be effective in the following dose schedules for the prevention of emesis during the first 24 hours following chemotherapy:

Initial Dose:

Ondansetron Injection USP 8 mg infused intravenously over 15 minutes given 30 minutes

prior to chemotherapy.

or

Ondansetron Injection USP 8 mg infused intravenously over 15 minutes, given 30 minutes prior to chemotherapy, followed by 1 mg/h by continuous infusion for up to 24 hours.

Or

Ondansetron Injection USP 32 mg diluted in 50-100 mL of saline or other compatible infusion fluid and infused over not less than 15 minutes[i], given 30 minutes prior to chemotherapy.

Post-chemotherapy:

No significant differences in terms of emesis control or grade of nausea have been demonstrated between the 32 mg single dose, the 8 mg single dose, or the 8 mg dose followed by the 24 hour 1 mg/h continuous infusion.

However, in some studies conducted in patients receiving medium or high doses of cisplatin chemotherapy, the 32 mg single dose has demonstrated a statistically significant superiority over the 8 mg single dose with regard to control of emesis.

The efficacy of ondansetron 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.

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 30 minutes prior to chemotherapy.

Use in Children:

Clinical experience of ondansetron 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 immediately before chemotherapy. For children 3 years of age and younger, there is insufficient information available to make dosage recommendations (see INDICATIONS AND CLINICAL USE).

[i] Infusion of 32 mg ondansetron injection (as hydrochloride dihydrate) should take place over a period of not less than 15 minutes, because of increased risk of blurred vision.

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.

Radiotherapy Induced Nausea and Vomiting:

Use in Children:

There is no experience in clinical studies in this population.

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 Ondansetron Injection USP may be administered as a single dose of 4 mg given by slow intravenous injection at induction of anaesthesia.

For the treatment of established post-operative nausea and vomiting, a single dose of 4 mg given by slow intravenous injection 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 (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 (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 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 USP is compatible with the following solutions:

For Ampoules
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.

For 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 USP should not be administered in the same syringe or infusion with any other medication with the exception of dexamethasone (see below). Ondansetron Injection USP 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 Ampoules and Vials:

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

For Ampoules:

Dexamethasone - admixtures containing 8 mg of ondansetron and 20 mg of dexamethasone phosphate, in 50 mL of 5% dextrose infusion fluid stored in 50 mL polyvinyl chloride infusion bags, have been shown to be physically and chemically stable for up to two days at room temperature or up to seven days at 2 - 8ºC. In addition, these same admixtures have demonstrated compatibility with Continu-Flo® administration sets.

In a clinical study (Cunningham et al, 1989) ondansetron (standard dosing regimen) was given to patients receiving cisplatin or non-cisplatin chemotherapy. Eight patients who continued to experience nausea and vomiting were given dexamethasone in addition to ondansetron. In every case there was an improvement in the control of emesis and all patients preferred the combination of ondansetron and dexamethasone.

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 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.

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. In all instances, the events resolved completely.

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.

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.

In a pharmacokinetic study of 16 epileptic patients maintained chronically on carbamazepine or phenytoin, reduction in AUC, Cmax and $T_{½}$ of ondansetron was observed. This resulted in a significant increase in clearance. However, on the basis of available data, no dosage adjustment is recommended (see WARNINGS AND PRECAUTIONS).

STORAGE AND STABILITY

Ondansetron Injection USP (as hydrochloride dihydrate) [preservative free]:

Ondansetron Injection USP should be stored between 15ºC – 30°C.

Ondansetron Injection USP should not be frozen and should be protected from light.
Injection must not be autoclaved.

Stability and Storage of Diluted Solutions:
Compatibility studies have been undertaken in polyvinyl chloride infusion bags, polyvinyl chloride administration sets and polypropylene syringes. Dilutions of ondansetron in sodium chloride 0.9% w/v or in dextrose 5% w/v have been demonstrated to be stable in polypropylene syringes. It is considered that Ondansetron Injection USP diluted with other compatible infusion fluids would be stable in polypropylene syringes.

Intravenous solutions should be prepared at the time of infusion. Ondansetron Injection USP, in ampoules, 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.

Hospitals and institutions that have recognized admixture programs and use validated aseptic techniques for preparation of intravenous solutions, may extend the storage time

for Ondansetron Injection USP in admixture with 5% Dextrose Injection and dexamethasone phosphate Injection (concentration of 0.34 mg/mL) in Viaflex® bags, at a concentration of 0.14 mg/mL, to 7 days when stored under refrigeration at 2°C to 8°C.

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

Ondansetron Injection USP (as hydrochloride dihydrate) [with preservatives]:

Ondansetron Injection USP should be stored between 15ºC – 30°C.

Ondansetron Injection USP should not be frozen and should be protected from light.
Injection must not be autoclaved.
The 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 USP 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.

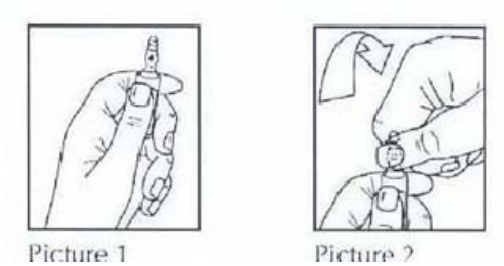
As with all parenteral drug products, intravenous admixtures should be inspected visually for clarity, particulate matter, precipitate, discolouration and leakage prior to administration, whenever solution and container permit. Solutions showing haziness, particulate matter, precipitate, discoloration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

SPECIAL HANDLING ISNTRUCTIONS

Ampoule Opening Instructions for Ondansetron Injection USP (2 mL and 4 mL ampoules)
Ampoules are equipped with One Point Cut opening system and must be opened using the following instructions:

Hold the bottom part of the ampoule in one hand with the dot facing you as indicated in picture 1.

Place the other hand on the top of the ampoule positioning the thumb on the dot. As indicated in picture 2, snap the top of the ampoule **away from you.**


Picture 1 Picture 2

DOSAGE FORMS, COMPOSITION AND PACKAGING

Ondansetron Injection USP (as hydrochloride dihydrate) [preservative free]:
Ondansetron Injection USP contains 2 mg/mL of ondansetron base, in the form of ondansetron hydrochloride dihydrate.

Ondansetron Injection USP (2 mL and 4 mL ampoules) also contains:

citric acid monohydrate	0.50 mg/mL
sodium citrate dihydrate	0.25 mg/mL
sodium chloride	9.00 mg/mL
water for injection	q.s. to 1 mL

Sodium hydroxide and/or hydrochloric acid may be used to adjust the pH to 3.30 – 4.00.

Ondansetron 2 mg/mL (as hydrochloride dihydrate) for intravenous use is supplied in 2 mL (4 mg) and 4 mL (8 mg) ampoules, in a plastic tray of 10 ampoules, packed in a carton.

Ondansetron Injection USP (as hydrochloride dihydrate) [with preservatives]:
Ondansetron Injection USP contains 2 mg/mL of ondansetron base, in the form of ondansetron hydrochloride dihydrate.

Ondansetron Injection USP (20 mL vial) also contains:

methylparaben (as preservative)	1.2 mg/mL
propylparaben (as preservative)	0.15 mg/mL
citric acid monohydrate	0.50 mg/mL
sodium chloride	8.3 mg/mL
sodium citrate dihydrate	0.25 mg/mL
water for injection	q.s. to 1 mL

Ondansetron 2 mg/mL (as ondansetron hydrochloride dihydrate) for intravenous use is supplied in 20 mL (40 mg) packed in individual cartons.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

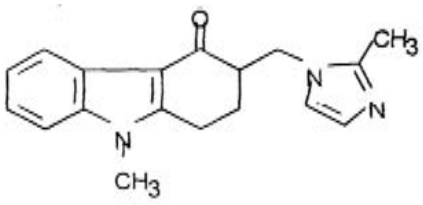
Proper name: ondansetron hydrochloride dihydrate

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:

$C_{18}H_{19}N_3O.HCl.2H_2O$ (hydrochloride dihydrate), 365.9 (hydrochloride hydrate)

Structural formula:



- $HCl.\ 2H_2O$

Physicochemical properties:
Description and Solubility:
Ondansetron is a white or almost white powder. It is sparingly soluble in water and in alcohol, soluble in methanol. The melting point of ondansetron is about 173° C. pKa is 7.4 and pH of 1% w/v solution in water is approximately 4.57.

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* 3 doses of 0.15 mg/kg	Placebo* 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%)	_	_	_

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

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

* 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 gynaecological surgery.

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

* 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 gynaecological surgery.

Prevention of Radiotherapy Induced Emesis – Response Over 24 Hours *			
		Oral Treatment	
Dose	Ondansetron 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 cm^2 to the abdomen.

*Patients received the first dose of ondansetron 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.

The antiemetic effects of ondansetron (0.1 mg/kg) in combination with dexamethasone (2-5 mg/kg) were potentiated in ferrets with cyclophosphamide-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, GABAA, 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 0.01-0.1 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 (i.e, may be attainable with the 32 mg IV dose). In vivo, a lengthening of the QT interval has been observed in anesthetized cats following intravenous dosing, but at doses exceeding 100 times those effective pharmacologically in cats (0.1-1 μg/kg IV). Similar effects were not seen in cynomolgus monkeys (at 0.1-3 mg/kg IV). Transient ECG changes have been reported in the clinic (see WARNINGS AND PRECAUTIONS).

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 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	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]Ondansetron Injection USP

2 mg/mL ondansetron (as ondansetron hydrochloride dihydrate)
Sterile solution

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. 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 (ondansetron hydrochloride dihydrate). This medicine is one of a group called antiemetics.

Ondansetron Injection USP is used for:
- the prevention of nausea (feeling of sickness) and vomiting associated with emetogenic chemotherapy and radiotherapy.
- the prevention and treatment of post-operative nausea and vomiting.

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. 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 nonmedicinal ingredients are) in Ondansetron Injection USP.
- if you are pregnant, or likely to become pregnant, or if you are breast feeding a baby. However, there may be circumstances when your doctor advises you to use this medicine during pregnancy.
- if you are taking apomorphine (used to treat Parkinson's disease).

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

What the nonmedicinal ingredients are:

Ondansetron Injection USP (as hydrochloride dihydrate) [preservative free]:
Ondansetron Injection USP (2 mL and 4 mL ampoules) contains the following nonmedicinal ingredients: citric acid monohydrate, sodium chloride, sodium citrate dihydrate, sodium hydroxide, hydrochloric acid and water for injection.

Ondansetron Injection USP (as hydrochloride dihydrate) [with preservatives]:
Ondansetron Injection USP (20 mL vial) contains the following nonmedicinal ingredients: methylparaben (as preservative), propylparaben (as preservative), citric acid monohydrate, sodium chloride, sodium citrate dihydrate and water for injection.

What dosage forms it comes in:

Ondansetron Injection USP (as hydrochloride dihydrate) [preservative free]:
Ondansetron 2 mg/mL (as hydrochloride dihydrate) for intravenous use is supplied in 2 mL (4 mg) and 4 mL (8 mg) ampoules, in a plastic tray of 10 ampoules, packed in a carton.

Ondansetron Injection USP (as hydrochloride dihydrate) [with preservatives]:
Ondansetron 2 mg/mL (as ondansetron hydrochloride dihydrate) for intravenous use is supplied in 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.
- you are pregnant or likely to become pregnant.
- you are breast feeding a baby.
- 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, **tell your doctor immediately.**

INTERACTIONS WITH THIS MEDICATION

It is important that your doctor know about all your medication so that you get the best possible treatment. Tell your doctor about all the medicines you are taking including those you have bought yourself. If you are taking any medicines containing tramadol, Ondansetron Injection USP may decrease its effectiveness.

PROPER USE OF THIS MEDICATION

Ondansetron Injection USP 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 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 for you.

Adult: The dose of Ondansetron Injection USP will be between 8 and 32 mg before your chemotherapy, depending on the potential of your chemotherapy treatment to cause you to vomit and/or have nausea. You may also receive Ondansetron Injection USP after your chemotherapy. The total daily dose does not exceed 32 mg.

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 at the injection site.

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/ Symptoms	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 (sometimes a sudden loss of consciousness)	X
Very Rare	Eye problems such as temporary blindness	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 15°C – 30°C. It should not be frozen and it should be protected from light. Injection must not be autoclaved.

Intravenous solutions should be prepared at the time of infusion. Ondansetron Injection USP, 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 report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

***NOTE:** Should you require information related to the management of side effects, contact your health professional. 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 sponsor,

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