PRODUCT MONOGRAPH

[Pr]ONDANSETRON INJECTION, USP

2 mg/mL ondansetron (as hydrochloride dihydrate)

Sterile

Antiemetic
(5-HT_3 receptor antagonist)

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous	Liquid / 2 mg/mL ondansetron, 2 mL and 4 mL ampoule and single use vials	No preservative. *For a complete listing, see* **DOSAGE FORMS, COMPOSITION AND PACKAGING** *section.*
Intravenous	Liquid / 2 mg/mL ondansetron, 20 mL multiple-dose vials	Contains preservatives: methylparaben and propylparaben *For a complete listing, see* **DOSAGE FORMS, COMPOSITION AND PACKAGING** *section.*

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 postoperative nausea and vomiting.

Pediatrics (< 18 years of age)

Postchemotherapy

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.

Postradiotherapy
Safety and efficacy of ondansetron in any age group in this population following radiotherapy have not been established and ondansetron is therefore not indicated for use in this population.

Postoperative Nausea and Vomiting
Safety and efficacy of ondansetron in any age group in this population for the prevention and treatment of postoperative nausea and vomiting have not been established, and ondansetron is not indicated for use in this group.

Geriatrics (> 65 years of age)

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

Postoperative Nausea and Vomiting
Clinical experience in the use of ondansetron in the prevention and treatment of postoperative nausea and vomiting is limited, and ondansetron is not indicated for use in this population.

CONTRAINDICATIONS

- Ondansetron Injection, USP 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.

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 and predominantly with intravenous ondansetron, transient ECG changes including QT interval prolongation have been reported (see **ADVERSE REACTIONS, Postmarket Adverse Drug Reactions**).

Ondansetron Injection, USP is not effective in preventing motion-induced nausea or 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 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

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.

Postmarket 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 postapproval use of ondansetron, although the link to ondansetron cannot always be clearly established.

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 QT interval prolongation 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 postoperative 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 i.v. infusion of ondansetron.

Uncommon reports (< 1%) suggestive of extrapyramidal reactions such as 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, frusemide, 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.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Chemotherapy-induced Nausea and Vomiting:

Ondansetron Injection, USP 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 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 **DOSAGE AND ADMINISTRATION, 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 Injection 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 8 mg infused intravenously over 15 minutes given 30 minutes prior to chemotherapy;

or

Ondansetron Injection 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 32 mg diluted in 50 - 100 mL of saline or other compatible infusion fluid and infused over not less than 15 minutes[1], given 30 minutes prior to 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.

[1] Infusion of 32 mg Ondansetron Injection should take place over a period of not less than 15 minutes, because of increased risk of blurred vision.

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

Initial Dose: Ondansetron Injection 8 mg infused intravenously over 15 minutes, given 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 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 or younger, there is insufficient information available to make dosage recommendations (see **INDICATIONS AND CLINICAL USE**).

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

Postoperative Nausea and Vomiting:

Use in Adults: For prevention of postoperative nausea and vomiting, Ondansetron Injection may be administered as a single dose of 4 mg given by slow intravenous injection at induction of anesthesia.

For the treatment of established postoperative 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 postoperative 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 postoperative 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 or frequency of dosing 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 or debrisoquine.

Administration

Administration of Intravenous Infusion Solutions

Compatibility with Intravenous Solutions:

Ondansetron Injection, USP (preservative-free formulation) is compatible with the following solutions:

5% w/v Dextrose Injection;
0.9% w/v Sodium Chloride Injection;
10% w/v Mannitol Injection;
Ringer's 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;
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;
3% w/v Sodium Chloride Injection.

Ondansetron Injection, USP (preservative-containing formulation) is compatible with the following solutions:

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

Compatibility with Other Drugs: Ondansetron Injection should not be administered in the same syringe or infusion with any other medication. Ondansetron Injection may be administered by intravenous infusion at 1 mg/hour, e.g., from an infusion bag or syringe pump.

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

Ondansetron Injection Preservative-free and Preservative Containing Formulations:
Cisplatin – concentrations up to 0.48 mg/mL administered over 1 to 8 hours.

Ondansetron Injection Preservative-free Formulation:
5-Fluorouracil – concentrations up to 0.8 mg/mL, administered at rates of at least 20 mL/hour. Higher concentrations of 5-fluorouracil may cause precipitation of ondansetron. The 5-fluorouracil infusion may contain up to 0.045% w/v magnesium chloride.

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

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

Cyclophosphamide – bolus i.v. 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 i.v. 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

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 antiemetic action of ondansetron itself.

"Sudden blindness" (amaurosis) of 2 to 3 minutes duration plus severe constipation occurred in one patient who was administered 72 mg of ondansetron intravenously as a single dose. Hypotension (and faintness) occurred in another patient who 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.

For management of a suspected drug overdose, contact your Regional Poison Control Centre immediately.

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 postoperative 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

An 8 mg infusion of ondansetron resulted in peak plasma levels of 80 - 100 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 i.v. administration, ondansetron is extensively metabolised and excreted in the urine and feces. 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 an 8 mg 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, C_{max} 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 should be stored between 15 and 30˚C. Ondansetron Injection should not be frozen and should be protected from light. Ondansetron 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 glucose 5% w/v have been demonstrated to be stable in polypropylene syringes. It is considered that ondansetron injection diluted with other compatible infusion fluids would be stable in polypropylene syringes.

Intravenous solutions should be prepared at the time of infusion. Ondansetron Injection 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 of Ondansetron Injection in admixture with 5% Dextrose Injection in Viaflex bags, at a concentration of 0.14 mg/mL, to 7 days when stored under refrigeration between 2 and 8˚C.

Single-dose vial: Discard unused portion.
Multiple-dose vial: Discard 28 days after initial puncture.

As with all parenteral 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, discolouration or leakage should not be used.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Availability:
Ondansetron Injection, USP 2 mg/mL (as hydrochloride dihydrate) is supplied in 2 mL (4 mg) and 4 mL (8 mg) preservative-free ampoules, in boxes of 5 ampoules; in 2 mL (4 mg) and 4 mL (8 mg) preservative-free single-dose vials, in boxes of 5 vials; and in 20 mL (40 mg) preservative-containing multiple-dose vials, packed in individual cartons.

Composition:
Ondansetron Injection, USP contains 2 mg/mL of ondansetron base, in the form of ondansetron hydrochloride dihydrate.

Ondansetron Injection, USP (preservative-free formulation) also contains:

sodium chloride	9 mg/mL
citric acid (anhydrous)	0.5 mg/mL
sodium citrate (dihydrate)	0.25 mg/mL

Ondansetron Injection, USP (preservative-containing formulation) also contains:

citric acid (monohydrate)	0.5 mg/mL
sodium citrate (dihydrate)	0.25 mg/mL
sodium chloride	8.3 mg/mL
methylparaben	1.2 mg/mL
propylparaben	0.15 mg/mL

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

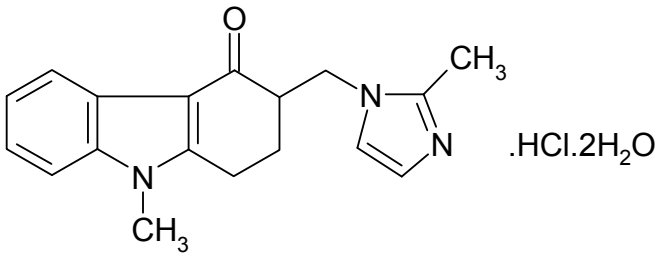
Drug Substance

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

Structural formula:



Physicochemical properties: 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 postoperative 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 POSTOPERATIVE EMESIS – RESPONSE OVER 24 HOURS*			
	INTRAVENOUS PREVENTION		
DOSE	**Ondansetron 4 mg IV**	**Placebo**	**p Value**
# of patients	136	139	
Treatment Response			
0 emetic episodes	103 (76%)	62 (46%)	< 0.001

*The majority of patients included in the prevention of postoperative nausea and vomiting studies using ondansetron have been adult women receiving balanced anesthesia for gynecological surgery.

TREATMENT OF POSTOPERATIVE 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 treatment of postoperative nausea and vomiting studies using ondansetron have been adult women receiving balanced anesthesia 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 - 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.

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

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-dependant 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. The concentration at which this effect was seen may be attainable with the 32 mg i.v. dose; however, the clinical relevance of this finding is uncertain.

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 i.v. 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 the 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 esophageal motility.

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 esophagus in some subjects.

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

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 postdosing 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
Dogs	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 postmitochondrial metabolizing system.

There was also no evidence of damage to genetic material noted *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 postnatal 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 postnatal 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]ONDANSETRON Injection, USP
2 mg/mL ondansetron (as ondansetron hydrochloride dihydrate)
Sterile

This leaflet is part III of a three-part "Product Monograph" published when Ondansetron Injection, USP was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Ondansetron Injection. Contact your doctor or pharmacist if you have any questions about the drug.

Ondansetron Injection can only be obtained with a prescription from your doctor.

ABOUT THIS MEDICATION

What the medication is used for:
The name of your medicine is Ondansetron Injection, USP. This medicine is one of a group of medicines called antiemetics.

Ondansetron is used for:

- the prevention of nausea (feeling of sickness) and vomiting associated with emetogenic chemotherapy, and radiotherapy;
- the prevention and treatment of postoperative nausea and vomiting.

What it does:
Treatments such as general anesthesia, 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 helps to stop this from happening, thus preventing you from vomiting or feeling sick.

When it should not be used:
Do not take ondansetron if:

- you have a history of hypersensitivity (an allergic reaction) to any ingredient (see "What the important nonmedicinal ingredients are") in the product;
- 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.

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

What the important nonmedicinal ingredients are:
Ondansetron Injection, USP (preservative-free formulation, 2 mL and 4 mL ampoules and single-dose vials) contains: sodium chloride, citric acid (anhydrous), sodium citrate (dihydrate), water for injection.

Ondansetron Injection, USP (preservative-containing formulation, 20 ml multiple-dose vials) contains: citric acid (monohydrate), methylparaben, propylparaben, sodium chloride, sodium citrate (dihydrate).

What dosage forms it comes in:
Ondansetron Injection, USP 2 mg/mL (as hydrochloride dihydrate) preservative-free formulation is supplied in 2 mL (4 mg) and 4 mL (8 mg) ampoules and single-dose vials, in boxes of 5 vials; and the preservative-containing formulation is supplied in 20 mL (40 mg) multiple-dose vial, packed in individual carton.

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;
- 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, **contact your doctor immediately. Do not take any more medicine unless your doctor tells you to do so.**

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 (such as TRAMACET), Ondansetron Injection, USP may decrease its effectiveness.

PROPER USE OF THIS MEDICATION

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

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

Usual dose:
Chemotherapy-induced Nausea and Vomiting
You will receive Ondansetron Injection, USP prior to chemotherapy. Based on how likely you are to experience nausea

and/or vomiting, caused by your cancer treatment, your doctor will tell you the amount you need to take and how frequently.

Adult: The dose of Ondansetron Injection will be between 8 and 32 mg a day depending on the potential of your chemotherapy treatment to cause you to vomit and/or have nausea.
Children (4 to 12 years): Just before chemotherapy, infuse 3 to 5 mg/m^2 over 15 minutes.

Postoperative Nausea and Vomiting
Adult: For prevention, 4 mg by slow i.v. injection at the induction of anesthesia. For treatment, 4 mg by slow i.v. injection.

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

Overdose:
In the event you accidentally take more doses than prescribed, immediately contact your doctor or hospital emergency department or nearest poison control centre.

In the event of overdosage, contact your doctor, hospital emergency department or regional Poison Control Centre.

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

If your nausea (feeling of sickness) or vomiting do not improve while taking Ondansetron Injection, 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

Symptom/effect		Talk with your doctor or pharmacist	Stop taking drug and call your doctor or pharmacist
Uncommon	Heart problems such as fast/slow heart beat, chest pain		✓
	Seizures	✓	
	Upward rolling of the eyes, abnormal muscular stiffness/body movements/ shaking		✓
Rare	Eye problems such as blurred vision	✓	
	Immediate allergic reaction and symptoms such as swelling of the mouth, throat, difficulty in breathing, rash, hives, increased heart rate		✓
Very Rare	Eye problems such as temporary blindness	✓	

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

HOW TO STORE IT

Ondansetron Injection, USP should be stored between 15 and 30˚C.

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

Intravenous solutions should be prepared at the time of infusion. Ondansetron Injection, 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 Report 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

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

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

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

This document plus the full product monograph, prepared for health professionals, can be requested from:

AGILA SPECIALTIES PRIVATE LIMITED

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