PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr ONDANSETRON OMEGA

Ondansetron Injection

Solution for injection, 2 mg/mL ondansetron
(as ondansetron hydrochloride dihydrate), intravenous

Omega Standard

Antiemetic (5-HT_3 receptor antagonist)

ATC code A04AA01

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RECENT MAJOR LABEL CHANGES

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Adults (18-64 years of age)
Ondansetron Omega (ondansetron hydrochloride dihydrate) is indicated for:

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

1.1 Pediatrics

Prevention of Nausea and Vomiting Associated with Highly Emetogenic Chemotherapy (e.g. cisplatin)

- **Pediatrics (<18 years of age):** Health Canada has not authorized an indication for pediatric use.

Prevention of Nausea and Vomiting Associated with Less Emetogenic Chemotherapy

- **Pediatrics (4-12 years of age):** Intravenous ondansetron was effective and well tolerated when given to children 4-12 years of age (see 4.2 Recommended Dose and Dose Adjustment).
- **Pediatrics (<4 years of age):** Ondansetron Omega is not indicated for the treatment of children less than 4 years old.

Prevention and Treatment of Post-Operative Nausea and Vomiting

- Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Prevention of Nausea and Vomiting Associated with Emeteogenic Chemotherapy

Efficacy and tolerance of ondansetron hydrochloride dihydrate were similar to that observed in younger adults (see 4.2 Recommended Dose and Dosage Adjustment, Chemotherapy induced Nausea and Vomiting, Use in Elderly; 7. WARNINGS AND PRECAUTIONS, Cardiovascular; 7.1.4 Geriatrics; 10.3 Pharmacokinetics, Geriatrics).

Prevention and Treatment of Post-Operative Nausea and Vomiting
Clinical experience in the use of intravenous ondansetron in the prevention and treatment of post-operative nausea and vomiting is limited; Ondansetron Omega is not indicated for this use in the geriatric population.

2 CONTRAINDICATIONS

- Ondansetron Omega (ondansetron hydrochloride dihydrate) is contraindicated in patients with a history of hypersensitivity to the drug or any components of its formulation. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

- The concomitant use of apomorphine with ondansetron is contraindicated based on reports of profound hypotension and loss of consciousness when apomorphine was administered with ondansetron.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Visually inspect IV solutions and discard if particulate matter or discolouration are observed. See 4.4 Administration.

Ondansetron Omega clearance is reduced in patients with moderate or severe hepatic impairment. Their total daily dose should not exceed 8 mg, which may be given as a single intravenous dose. See 7 WARNINGS AND PRECAUTIONS, Hepatic.

Ondansetron hydrochloride dihydrate has important cardiac side-effects (dose-dependent QTc prolongation, coronary artery spasm, myocardial ischemia, and sequelae). These effects are reported more often with intravenous administration, and are expected to be greater with a faster rate of infusion. See 7 WARNINGS AND PRECAUTIONS, Cardiovascular, QTc Interval Prolongation; and Myocardial Ischemia and Coronary Artery Spasm; 9.4 Drug-Drug Interactions, QTc-Prolonging Drugs; 10.2 Pharmacodynamics, Electrocardiography.

Though ondansetron hydrochloride dihydrate efficacy and tolerance were similar for elderly compared to younger adults in chemotherapy clinical trials, exposure-response modelling predicted a greater effect on QTcF in patients ≥75 years of age compared to young adults. See 10.3 Pharmacokinetics, Geriatrics.

Dosing considerations that reduce cardiac risks:

- Carefully follow the dosing guidelines
- Use the minimum effective dose.
- Consider use of an oral ondansetron formulation (lower Cmax). **Note: Ondansetron**

Omega is only available as a solution for injection.

- **Infuse slowly,** over a minimum of 15 minutes.
- Maximum IV dose is 16 mg (adults).
- **Consider ECG monitoring** if treating elderly patients with an IV dose of 16 mg. There is an increased risk for slight QTcF interval prolongation above 10 ms (from baseline) for about 10 min.
- **Dilute the IV dose** in 50 mL to 100 mL of 0.9% Sodium Chloride Injection or 5% Dextrose Injection (see 4.4 Administration):
    - Elderly (age ≥65 years): all IV doses
    - Adults (age <65 years): IV doses >8 mg.
- Following initial dosing, do not shorten the recommended interval between subsequent IV infusions (e.g. at 4 and 8 hours). Cardiac side effects have been reported after subsequent dosing.

The efficacy of Ondansetron Omega 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.

4.2 Recommended Dose and Dosage Adjustment

Prevention of Highly Emetogenic Chemotherapy Induced Nausea and Vomiting

Caution: To reduce cardiac risks, carefully follow the dosing guidelines under 4.1 Dosing Considerations.

- ***Adults***
    - Initial IV dose of 8 mg (max 16 mg) infused over 15 minutes, given at least 30 minutes prior to chemotherapy

      Or
    - Initial IV dose of 8 mg (max 16 mg) infused over 15 minutes, given at least 30 minutes prior to chemotherapy, followed by two additional IV doses of 8 mg given at 4 and 8 hours after the initial dose.

For maintenance of anti-emesis beyond the first 24 hours, patients should be switched to an oral formulation. **Note: Ondansetron Omega is only available as a solution for injection.**

- ***Pediatrics (<18 years of age)***

- Ondansetron Omega is not approved for this use in children.

- ***Geriatrics***
  Efficacy and tolerance in patients 65 years of age and older were similar to that seen in younger adults. No dosage adjustment is required in this population (see 7.1.4 Geriatrics; 10.3 Pharmacokinetics, Geriatrics).

- **Hepatic Insufficiency**
  No dosage adjustment is needed in patients with mild hepatic impairment.
  In patients with moderate or severe hepatic impairment (Child-Pugh score ≥ 7), do not exceed a total daily dose of 8 mg (Child-Pugh score of 10 or greater) (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic; 10.3 Pharmacokinetics). This may be given as a single intravenous dose.

- **Renal Insufficiency**
  No alteration of daily dosage, frequency of dosing, or route of administration is required in patients with impaired renal function (see 10.3 Pharmacokinetics, Renal Insufficiency).

Prevention of Less Emetogenic Chemotherapy Induced Nausea and Vomiting

Caution: To reduce cardiac risks, carefully follow the dosing guidelines under 4.1 Dosing Considerations.

- ***Adults:***
  - Initial IV dose 8 mg, infused over 15 minutes, given 30 minutes before chemotherapy.

For maintenance of anti-emesis beyond the first 24 hours, patients should be switched to an oral formulation. **Note: Ondansetron Omega is only available as a solution for injection.**

- ***Pediatrics (4 - < 18 years of age)***
  - Initial IV dose 3 to 5 mg/m^2, infused over 15 minutes, at least 30 minutes before chemotherapy.

- ***Pediatrics (<4 years of age)***
  Ondansetron Omega is not indicated for this use in children under 4 years of age.

- ***Geriatrics (65-74 years of age):***
  - Initial IV dose of 8 mg (max 16* mg), diluted (see 4.4 Administration), infused over 15 minutes, given at least 30 minutes prior to chemotherapy.

- May be followed by two IV doses of 8 mg, diluted, infused over 15 minutes, at least 4 hours apart.

* **When the initial dose is 16 mg**, there is a predicted increase of the risk for a slight QTcFinterval prolongation above 10 ms (from baseline) for about 10 min. ECG monitoring may be considered.

- ***Geriatrics (≥75 years of age):***
  - Initial IV dose: should be 8 mg maximum, diluted, infused over 15 minutes, given at least 30 minutes prior to chemotherapy.
  - May be followed by two IV doses** of 8 mg, diluted (see 4.4 Administration), infused over 15 minutes, at least 4 hours apart.

** **For the third dose**, there is a predicted increase of the risk for a slight QTcF intervalprolongation above 10 ms (from baseline) for about 10 min. ECG monitoring may beconsidered.

- **Hepatic Insufficiency**
  No dosage adjustment is needed in patients with mild hepatic impairment.
  In patients with moderate or severe hepatic impairment (Child-Pugh score ≥ 7), do not exceed a total daily dose of 8 mg (Child-Pugh score of 10 or greater) (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic; 10.3 Pharmacokinetics). This may be given as a single intravenous dose.

- **Renal Insufficiency**
  No alteration of daily dosage, frequency of dosing, or route of administration is required in patients with impaired renal function (see 10.3 Pharmacokinetics, Renal Insufficiency).

Prevention and Treatment of Post-Operative Nausea and Vomiting

- ***Adults:***
  - Prevention: 4 mg IV, undiluted and infused - preferably over 2-5 minutes, and not less than 30 seconds, at induction of anesthesia.
  - Treatment: a single dose of 4 mg IV, infused - preferably over 2-5 minutes, and not less than 30 seconds.

- ***Pediatrics (<18 years of age):***

Health Canada has not authorized an indication for the prevention or treatment of post-

operative nausea and vomiting in children.

- ***Geriatrics (≥65 years of age):***
  Health Canada has not authorized an indication for the prevention or treatment of post-operative nausea and vomiting in geriatric patients.

- **Hepatic Insufficiency**
  No dosage adjustment is needed in patients with mild hepatic impairment.
  In patients with moderate or severe hepatic impairment (Child-Pugh score ≥ 7), do not exceed a total daily dose of 8 mg (Child-Pugh score of 10 or greater) (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic; 10.3 Pharmacokinetics). This may be given as a single intravenous dose.

- **Renal Insufficiency**
  No alteration of daily dosage, frequency of dosing, or route of administration is required in patients with impaired renal function (see 10.3 Pharmacokinetics, Renal Insufficiency).

4.4 Administration

Administration of Intravenous Infusion Solutions

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. See also 11. STORAGE, STABILITY AND DISPOSAL, Stability and Storage of Diluted Solutions.

All IV doses for the elderly, and IV doses over 8 mg for adults, should be diluted in 50-100 ml of 0.9% Sodium Chloride Injection or 5% Dextrose Injection.

Compatibility with Intravenous Solutions:

Ondansetron Omega should only be mixed with the infusion solutions recommended below:

<u>For single use vials</u>:
0.9% w/v Sodium Chloride Injection;

5% w/v Dextrose Injection.

For multiple dose 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.

Compatibility with Other Drugs:

Ondansetron Omega should not be administered in the same syringe or infusion with any other medication.

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.

- **Cisplatin** - concentrations up to 0.48 mg/mL administered over 1 to 8 hours.
- **5-Fluorouracil** - concentrations up to 0.8 mg/mL, administered at rates of at least 20 mL/hour. Higher concentrations of 5-fluorouracil may cause precipitation of ondansetron. The 5-fluorouracil infusion may contain up to 0.045% w/v magnesium chloride.
- **Carboplatin** - concentrations of 0.18 mg/mL - 9.9 mg/mL, administered over 10 – 60 minutes.
- **Ceftazidime** - bolus IV doses, over approximately 5 minutes, of 250 – 2000 mg reconstituted with Water for Injections BP.
- **Cyclophosphamide** - bolus IV doses over approximately 5 minutes, of 100 – 1000 mg, reconstituted with Water for Injections BP 5 mL per 100 mg cyclophosphamide.
- **Doxorubicin and Epirubicin** - bolus IV doses, over approximately 5 minutes, of 10-100 mg as a 2 mg/mL solution. Lyophilized powder presentations can be reconstituted with 0.9% Sodium Chloride Injection USP.
- **Etoposide** - concentrations of 0.144 mg/mL - 0.25 mg/mL, administered over 30 – 60 minutes.

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

Ondansetron prolongs QT interval in a dose-dependent fashion (see 10.2 Pharmacodynamics). ECG monitoring is recommended in cases of overdose.

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

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

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1– Dosage Forms, Strengths, Composition and Packaging

Route of Administration	**Dosage Form / Strength / Composition**	**Nonmedicinal Ingredients**	
Intravenous	Solution for Injection: 2 mg/mL ondansetron (as ondansetron hydrochloride dihydrate)	2 and 4 mL Single dose	20 mL Multidose
		citric acid monohydrate, sodium chloride, sodium citrate.	citric acid monohydrate, methylparaben, propylparaben, sodium chloride, sodium citrate.

Ondansetron Omega (single use and multiple dose vials) contains 2 mg/mL of ondansetron base, in the form of ondansetron hydrochloride dihydrate.

Ondansetron Omega (2 and 4 mL single use vials) also contains:

Citric Acid monohydrate	0.50 mg/mL
Sodium Citrate	0.25 mg/mL
Sodium Chloride	9.00 mg/mL

Ondansetron Omega (20 mL multiple dose vials) also contains:

Citric Acid monohydrate	0.50 mg/mL
Sodium Citrate	0.25 mg/mL
Sodium Chloride	8.30 mg/mL
Methylparaben	1.2 mg/mL
Propylparaben	0.15 mg/mL

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

7 WARNINGS AND PRECAUTIONS

General

Ondansetron Omega is not effective in preventing motion-induced nausea and vomiting.

Cardiovascular

QTc Interval Prolongation: Ondansetron prolongs the QT interval (see 10.2 Pharmacodynamics, Electrocardiography). The magnitude of QTc prolongation will depend on the peak serum ondansetron concentration (Cmax), which is substantially determined by the route of administration, the dose and the infusion rate of intravenous ondansetron. In addition, post-marketing cases of Torsade de Pointes have been reported in patients using ondansetron. Torsade de pointes is a polymorphic ventricular tachyarrhythmia. Generally, the risk of torsade de pointes increases with the magnitude of QTc prolongation produced by the drug. Torsade de pointes may be asymptomatic or experienced by the patient as dizziness, palpitations, syncope, or seizures. If sustained, torsade de pointes can progress to ventricular fibrillation and sudden cardiac death.

Avoid ondansetron in patients with congenital long QT syndrome. Ondansetron should be administered with caution to patients who have or may develop prolongation of QTc, including

congestive heart failure, bradyarrhythmias or patients taking other medicinal products that lead to either QT prolongation or electrolyte abnormalities (see 9.4 Drug-Drug Interactions).

Hypokalemia, hypocalcaemia, and hypomagnesaemia should be corrected prior to ondansetron administration.

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

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

Myocardial Ischemia and Coronary Artery Spasm: Ondansetron can cause coronary artery vasospasm and myocardial ischemia which may lead to myocardial infarction. In some cases, the symptoms appeared immediately after IV infusion or shortly after oral administration, including after low doses in patients without significant known pre-existing cardiovascular disease or other risk factors. Caution is advised during and after ondansetron administration, and close monitoring is recommended in patients with known or suspected ischemic or vasospastic coronary artery disease or other significant underlying cardiovascular disease.

Driving and Operating Machinery
In psychomotor testing ondansetron does not impair performance nor cause sedation.

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

Hepatic/Biliary/Pancreatic
Abnormal liver function test results have been reported, as well as liver failure in clinical trial cancer patients. See 8.2 Clinical Trial Adverse Reactions, Hepatic; and 8.5 Post-Market Adverse Reactions.

Immune
Cross-reactive hypersensitivity has been reported between different 5-HT_3 antagonists. Patients who have experienced hypersensitivity reactions to one 5-HT_3 antagonist have experienced more severe reactions upon being challenged with another drug of the same class. The use of a different 5-HT_3 receptor antagonist is not recommended as a replacement in cases in which a patient has experienced even a mild hypersensitivity type reaction to another 5-HT_3 antagonist.

Neurologic
Serotonin Toxicity / Neuroleptic Malignant Syndrome:

On rare occasions, serotonin toxicity, also known as serotonin syndrome, has been reported with ondansetron, particularly during combined use with other serotonergic drugs (See 9.4 Drug-Drug Interactions).

Serotonin toxicity is characterized by neuromuscular excitation, autonomic stimulation (e.g. tachycardia, flushing) and altered mental state (e.g. anxiety, agitation, hypomania). In accordance with the Hunter criteria, serotonin toxicity diagnosis is likely when, in the presence of at least one serotonergic agent, one of the following is observed:

- Spontaneous clonus
- Inducible clonus or ocular clonus with agitation or diaphoresis
- Tremor and hyperreflexia
- Hypertonia and body temperature > 38˚C and ocular clonus or inducible clonus

Neuroleptic malignant syndrome has also been rarely reported with ondansetron, particularly during combined use with neuroleptic/antipsychotic drugs. The clinical manifestations of neuroleptic malignant syndrome often overlap with those of serotonin toxicity, including hyperthermia, hypertonia, altered mental status, and autonomic instability. In contrast to serotonin toxicity, patients with neuroleptic malignant syndrome may present with “lead pipe” muscle rigidity as well as hyporeflexia.

Ondansetron should be used with caution in patients receiving other serotonergic drugs or antipsychotics/neuroleptics. If concomitant treatment with ondansetron, and other serotonergic drugs and/or antipsychotics/neuroleptics is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see 9.4 Drug-Drug Interactions). Serotonin toxicity and neuroleptic malignant syndrome may result in potentially life-threatening conditions. If serotonin toxicity or neuroleptic malignant

syndrome is suspected, discontinuation of Ondansetron Omega, should be considered.

Reproductive Health: Female and Male Potential
Pregnancy status should be verified for females of reproductive potential prior to starting treatment with Ondansetron Omega.

Females of reproductive potential should be advised of the possible harm Ondansetron Omega can cause to the developing foetus. Sexually active females of reproductive potential should use effective contraception (methods that result in less than 1% pregnancy rates) when using Ondansetron Omega and for two days after stopping treatment with Ondansetron Omega.

7.1 Special Populations

7.1.1 Pregnant Women

The use of ondansetron during pregnancy is not recommended.

Ondansetron use during early pregnancy has been associated with a small increase in orofacial malformations. Despite some limitations in methodology, several human epidemiological studies have noted an increase in orofacial clefts in infants of women administered ondansetron during the first trimester of pregnancy. Regarding cardiac malformations, the epidemiological studies showed conflicting results.

Ondansetron is not teratogenic in animals (see 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology).

7.1.2 Breast-feeding

Ondansetron is excreted in the milk of lactating rats. It is not known if it is excreted in human milk, however, breast-feeding is not recommended during treatment with ondansetron.

7.1.3 Pediatrics

Insufficient information is available to inform dosage recommendations for children 3 years of age or younger. Ondansetron Omega is not indicated for use in children less than 4 years of age (see 1.1 Pediatrics (<18 years of age)).

7.1.4 Geriatrics

Early Phase I studies in healthy elderly volunteers showed a slight age-related decrease in clearance, and an increase in half-life of ondansetron. A greater effect on QTcF is predicted in patients ≥75 years of age compared to young adults, based on exposure-response modelling. See 10.3 Pharmacokinetics, Geriatrics.

8 ADVERSE REACTIONS

8.2 Clinical Trials Adverse Reactions

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

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

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

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

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

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

Eye Disorder:
There have been reports of transient visual disturbances, including blurred vision and, in very rare cases, transient blindness, during or shortly after ondansetron treatment. These were observed generally within the recommended dosing range and predominantly during intravenous administration.

Hepatic/ Biliary / Pancreatic
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.

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 have been rare reports of hypokalemia.

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

8.5 Post-Market Adverse Reactions

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

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

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

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

Rarely and predominantly with intravenous ondansetron, transient ECG changes including QTc interval prolongation, Torsade de Pointes, ventricular fibrillation, coronary artery spasm, myocardial ischemia, cardiac arrest, and sudden death have been reported (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular).

Eye Disorder
There have been very rare cases of transient blindness following ondansetron treatment,

generally within the recommended dosing range and predominantly during intravenous administration.

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

Hepatic/ Biliary / Pancreatic
Occasional asymptomatic increases in liver function tests have been reported.

Nervous System Disorders
Transient episodes of dizziness (< 0.1%) have been reported predominantly during or upon completion of I.V. infusion of ondansetron.

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

Serotonin syndrome and neuroleptic malignant syndrome-like events have been reported with 5-HT3 receptor antagonist antiemetics, including ondansetron hydrochloride dihydrate, when given in combination with other serotonergic and/or neuroleptic drugs (see 7 WARNINGS AND PRECAUTIONS, Neurologic).

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

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

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions (see 9.4 Drug-Drug Interactions)

- Apomorphine (see 2 CONTRAINDICATIONS)
- QTc-prolonging drugs
- serotonergic agents

9.2 Drug Interactions Overview

Ondansetron is extensively metabolised by multiple hepatic cytochrome P450 enzymes (predominantly CYP3A4, also CYP2D6 and CYP1A2), and clearance is reduced in hepatic insufficiency (see 10.3 Pharmacokinetics, Hepatic Insufficiency). CYP 3A4 inducers can increase ondansetron clearance (see 9.4. Drug-Drug Interactions, CYP 3A4 Inducers).

Ondansetron does not itself appear to induce or inhibit the cytochrome P450 drug-metabolizing enzyme system of the liver.

9.3 Drug-Behavioural Interactions

Potential interactions, in terms of individual behavioural risks, have not been established.

9.4 Drug-Drug Interactions

CYP 3A4 inducers: Patients treated with inducers of CYP3A4 (i.e. phenytoin, carbamazepine, and rifampicin) demonstrated an increase in clearance of oral ondansetron and a decrease in ondansetron blood concentrations.

In a pharmacokinetic study of 16 epileptic patients maintained chronically on carbamazepine or phenytoin (CYP 3A4 inducers), reduction in AUC, C_{max} and $T_{½}$ of ondansetron was observed. This resulted in a significant increase in clearance. However, no dosage adjustment can be recommended, due to inter-subject variability in the available data.

Cytochrome P450 Inhibitors: No effect on ondansetron clearance secondary to enzyme inhibition or reduced activity (e.g. CYP 2D6 genetic deficiency) has been identified to date.

QTc-Prolonging Drugs: The concomitant use of ondansetron with another QTc-prolonging drug should be carefully considered to determine that the therapeutic benefit outweighs the potential risk (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular; 9.1 Serious Drug Interactions). Drugs that have been associated with QTc interval prolongation and/or torsade de pointes include, but are not limited to, the examples in the following list. Chemical/pharmacological classes are listed if some, although not necessarily all, class members have been implicated in QTc prolongation and/or torsade de pointes:

- Class IA antiarrhythmics (e.g., quinidine, procainamide, disopyramide);
- Class III antiarrhythmics (e.g., amiodarone, sotalol, ibutilide, dronedarone);
- Class 1C antiarrhythmics (e.g., flecainide, propafenone);

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

Drugs that Cause Electrolyte Abnormalities: The use of Ondansetron Omega with drugs that can disrupt electrolyte levels should be avoided. Such drugs include, but are not limited to, the following:

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

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

Apomorphine: Based on reports of profound hypotension and loss of consciousness when ondansetron was administered with apomorphine hydrochloride, concomitant use with apomorphine is contraindicated (see 2 CONTRAINDICATIONS; 9.1 Serious Drug Interactions)).

Serotonergic Drugs: As with other serotonergic agents, serotonin syndrome/toxicity, a potentially life- threatening condition, may occur with 5-HT_3 receptor antagonist antiemetic treatment when given in combination with other agents that may affect the serotonergic neurotransmitter system, including triptans, selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), other 5-HT_3 receptor antagonists, lithium, sibutramine, fentanyl and its analogues, dextromethorphan, tramadol, tapentadol, meperidine, methadone, pertazocine, St. John's Wort (*Hypericum perforatum*) and MAOIs, including phenlizine, moclobemide, tranylcypromine,

linezolid (an antibiotic which is a reversible non-selective MAOI) and methylene blue (see 7 WARNINGS AND PRECAUTIONS, Neurologic; 9.1 Serious Drug Interactions).

Antipsychotics/Neuroleptics: Neuroleptic malignant syndrome has been rarely reported with ondansetron, particularly during combined use with neuroleptic/antipsychotic drugs (e.g. haloperidol, olanzapine, quetiapine, risperidone) (see 7 WARNINGS AND PRECAUTIONS, Neurologic).

The above list of potential drug interactions is not comprehensive. Current information sources should be consulted for newly approved drugs that prolong the QTc interval, affect the serotonergic system, increase CYP 3A4 enzyme activity, or cause electrolyte disturbances, as well as for older drugs for which these effects have recently been established.

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

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

Exercise caution when using Ondansetron Omega with herbal products that may alter serotonin levels or act as CYP3A4 inducers/inhibitors, such as St. John's wort, ginseng, L-tryptophan, valerian, and Ginkgo biloba.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Ondansetron Omega (ondansetron hydrochloride dihydrate) 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.

10.2 Pharmacodynamics

Serotonin receptors of the 5-HT3 type are present both peripherally and on vagal nerve terminals. Ondansetron probably acts by preventing activation of these receptors or receptors located in other regions of the central nervous system. Both the peripheral and central nervous systems appear to be involved since both abdominal vagotomy and microinjection of ondansetron and other 5-HT3 antagonists directly into the area postrema eliminate cisplatin-induced emesis, while 5-HT1-like (methiothepin maleate) and 5-HT2 (ketanserin) antagonists have no effect.
Ondansetron is highly selective for 5-HT3 receptors and shows negligible binding to other receptors such as 5-HT1-like, 5-HT2, α1 and α2 adrenoceptors, β1 and β2 adrenoceptors, D1 and D2 muscarinic, nicotinic, GABAA, H1 and H2 receptors.

The pharmacological specificity of ondansetron may explain the observed lack of extrapyramidal side effects often seen following similar therapy with metoclopramide, which preferentially binds to dopamine receptors of the D2 subtype.
In vivo pharmacodynamic studies have investigated the effects of ondansetron on gastric emptying, small bowel transit time and oesophageal motility.

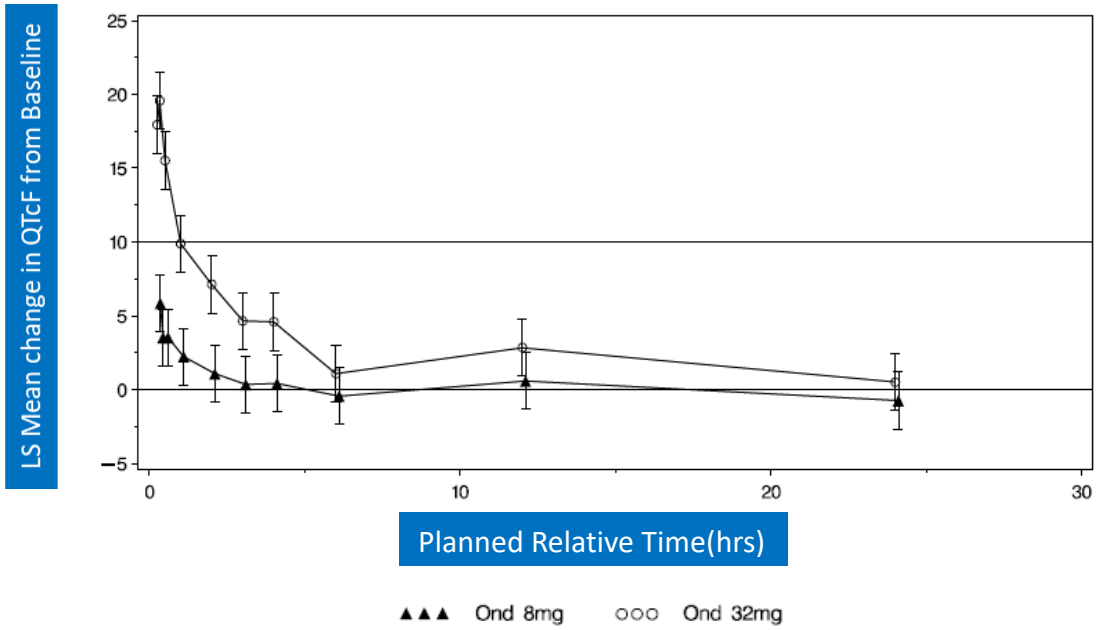
Both oral (16 mg tid) and intravenous (5-10 mg) doses of ondansetron failed to produce a significant effect on gastric emptying in both healthy volunteers and in patients suffering from delayed gastric emptying. However, in one study intravenous doses of 8 mg did increase gastric emptying in over half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

Electrocardiography
A study in cloned human cardiac ion channels has show ondansetron has the potential to affect cardiac repolarisation via blockade of hERG potassium channels at clinically relevant concentrations. Dose-dependent QT prolongation has been observed in a thorough QT study in human volunteers.

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

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

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



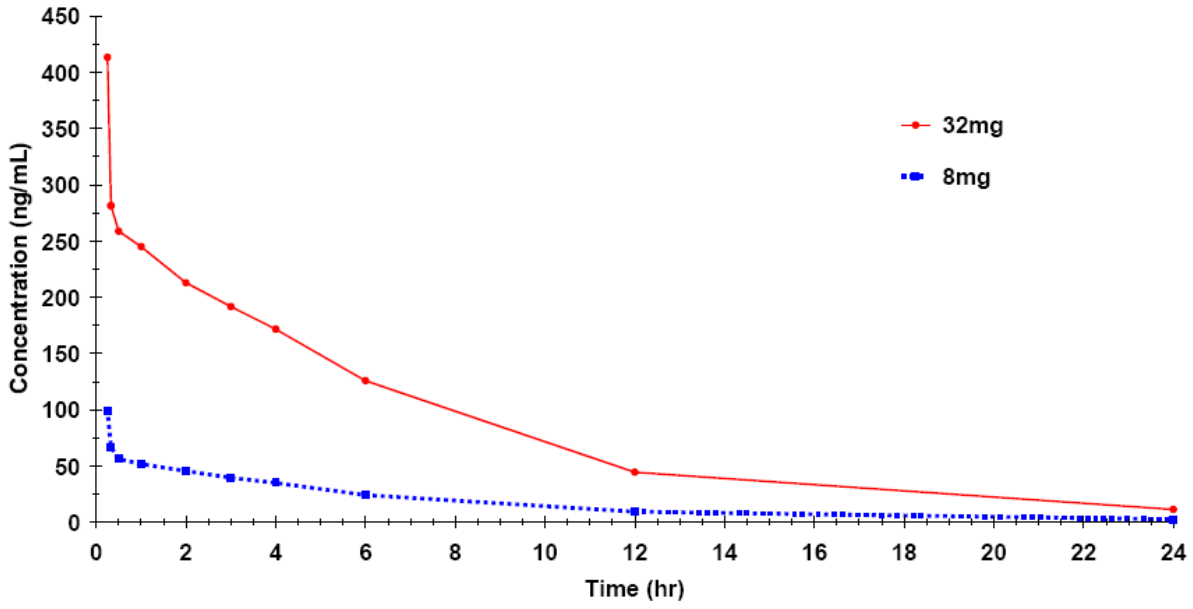
An ECG assessment study has not been performed for orally administered ondansetron. On the basis of pharmacokinetic-pharmacodynamic modelling, an 8 mg oral dose of ondansetron is predicted to cause a mean QTcF increase of 0.7 ms (90% CI -2.1, 3.3) at steady-state, assuming a mean maximal plasma concentration of 24.7 ng/mL (95% CI 21.1, 29.0).

The magnitude of QTc prolongation at the recommended 5 mg/m^2 dose in pediatrics has not been studied, but pharmacokinetic-pharmacodynamic modelling predicts a mean increase of 6.6 ms (90% CI 2.8, 10.7) at maximal plasma concentrations.

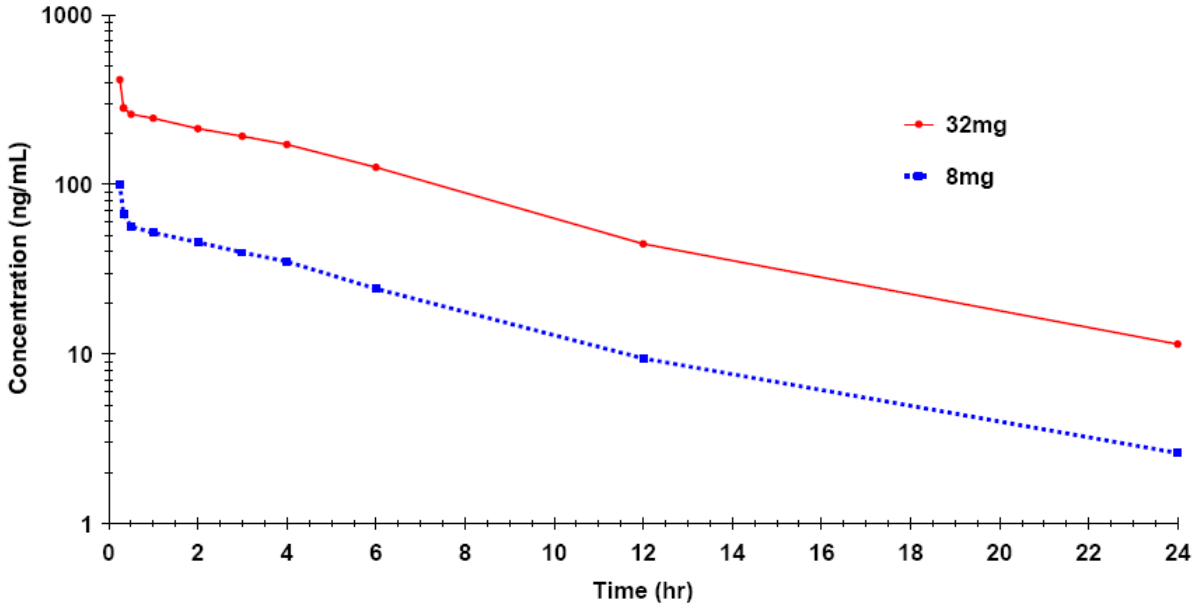
10.3 Pharmacokinetics

Absorption
Pharmacokinetic studies in human volunteers: 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.

Mean plasma concentration-time curves for ondansetron following 8 mg and 32 mg dose:
Linear Scale



Semi-logarithmic Scale



Distribution

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

See also 16. NON-CLINICAL TOXICOLOGY, Non-clinical pharmacokinetics.

Metabolism

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.

CYP 3A4 inducers can increase clearance (see 9.4 Drug-Drug Interactions, CYP 3A4 inducers).

Elimination

Following extensive metabolism of an orally or intravenously administered dose, ondansetron is 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%), sulfate 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.

Special Populations and Conditions

- **Geriatrics**

Early Phase I studies in healthy elderly volunteers showed a slight age-related decrease in clearance, and an increase in half-life of ondansetron. However, wide inter-subject variability resulted in considerable overlap in pharmacokinetic parameters between young (< 65 years of age) and elderly subjects (≥ 65 years of age) and there were no overall differences in safety or efficacy observed between young and elderly cancer patients enrolled in CINV clinical trials. (See 4.2 Recommended Dose and Dosage Adjustment, Use in Elderly). There is limited data involving patients ≥ 75 years of age.

Based on more recent ondansetron plasma concentrations and exposure-response modelling, a greater effect on QTcF is predicted in patients ≥75 years of age compared to young adults. Specific dosing information is provided for patients over 65 years of age and over 75 years of age for intravenous dosing. (See 4.2 Recommended Dose and Dosage Adjustment, Use in Elderly)

- **Genetic Polymorphism**

CYP 2D6: 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 (CYP 2D6 substrates). No alteration of daily dosage or frequency of ondansetron dosing is recommended for patients known to be CYP 2D6 poor metabolisers.

- **Hepatic Insufficiency**

Ondansetron is extensively metabolized by the liver. The clearance of an 8 mg intravenous dose of ondansetron hydrochloride dihydrate 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 (see 4.2 Recommended Dose and Dosage Adjustment).

There is no experience in patients who are clinically jaundiced.

- **Renal Insufficiency**

Renal impairment is not expected to significantly influence the total clearance of ondansetron, as renal clearance represents only 5% of the overall clearance. No dosage adjustment is required in patients with impaired renal function (see 4.2 Recommended Dose and Dose Adjustment).

11 STORAGE, STABILITY AND DISPOSAL

Ondansetron Omega should be stored between 15°C and 30°C.
Ondansetron Omega should not be frozen and should be protected from light.

Ondansetron Omega must not be autoclaved. 2-mL and 4-mL sizes are for single use, and unused portions of these should be discarded. The 20-mL size is for multiple uses and the vial content should be used within 28-days after first puncture. After this delay, the unused portion of the multiple uses format should be discarded.

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 diluted with other compatible infusion fluids would be stable in polypropylene syringes.

Intravenous solutions should be prepared at the time of infusion.
Ondansetron Omega, 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.
There is no specific instruction for disposal.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

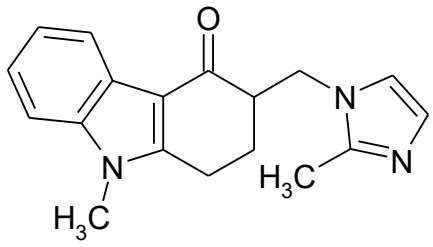
Drug Substance

Proper Name: Ondansetron Hydrochloride Dihydrate

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

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

Structural Formula:



x HCl x 2 H_2O

Physicochemical properties:

Description and Solubility:

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

log D = 2.2 at a pH of 10.60
log D = 0.6 at a pH of 5.95.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

The clinical trial data on which the original indication was authorized is not available.

14.2 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.

Table 2: PREVENTION OF CHEMOTHERAPY INDUCED EMESIS - RESPONSE OVER 24 HOURS					
DOSE	Ondansetron hydrochloride dihydrate * 3 doses of 0.15 mg/kg	Placebo* 3 doses of placebo	Ondansetron hydrochloride dihydrate 8 mg I.V. + 1 mg/hr, 24 hours	Ondansetron hydrochloride dihydrate 8 mg I.V.	Ondansetron hydrochloride dihydrate 32 mg I.V.
# 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.					

Table 3: PREVENTION OF POST-OPERATIVE EMESIS - RESPONSE OVER 24 HOURSδ						
	ORAL PREVENTION			INTRAVENOUS PREVENTION		
DOSE	Ondansetron hydrochloride dihydrate 16 mg od	Placebo	p Value	Ondansetron hydrochloride dihydrate 4 mg I.V.	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
δ 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 anesthesia for gynaecological surgery.						

Table 4: TREATMENT OF POST-OPERATIVE EMESIS - RESPONSE OVER 24 HOURS ‡			
	INTRAVENOUS TREATMENT		
DOSE	Ondansetron hydrochloride dihydrate 4 mg I.V.	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 anesthesia for gynaecological surgery.			

16 NON-CLINICAL TOXICOLOGY

Non-clinical Pharmacodynamics:

Ferret model: 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.

CINV: 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.

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

Gastric emptying: 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.

QT-prolongation: A study in cloned human cardiac ion channels has shown ondansetron has the potential to affect cardiac repolarisation via blockade of hERG potassium channels at clinically relevant concentrations. Dose-dependent QT prolongation has been observed in a thorough QT study in human volunteers (see 10.2 Pharmacodynamics, Electrocardiography).

Non-clinical 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 sulfate. 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.

General 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.

Table 5 - Acute Toxicity

Species	LD_{50} (mg/kg)	
	Oral	**I.V.**
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

Table 6 - Subacute Toxicity Studies

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

Table 7 - 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

Table 8 - 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

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.

Reproductive and Developmental Toxicology: 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; the maternal dose was approximately 6 and 24 times the maximum recommended human oral dose of 24 mg/day, respectively, based on body surface area). No adverse effects on pregnancy or fœtal and post-natal development were detected in rats and no fœtal 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 fœtal 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 fœtal exposure to low levels of ondansetron and its metabolites. Ondansetron is retained in the fœtal 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 (a maternal dose of approximately 6 times the maximum recommended human oral dose of 24 mg/day, based on body surface area) 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. Fœtal development of the F2 generation was comparable to controls; however, the number of implantations and viable fœtuses was reduced in the highest dosage group when compared with controls.

17 SUPPORTING PRODUCT MONOGRAPHS

1. PrZOFRAN® (Solution for injection, 2 mg/mL), submission control 252778, Product Monograph, Novartis Pharmaceuticals Canada Inc. (Nov 09, 2021).

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr] Ondansetron Omega
Ondansetron Injection

Read this carefully before you start taking **Ondansetron Omega** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Ondansetron Omega.**

What is Ondansetron Omega used for?

Children (4 to 17 years of age):
Ondansetron Omega is used to prevent nausea and vomiting during chemotherapy.

Adults (18 to 64 years of age):

Ondansetron Omega is used:

- to prevent nausea and vomiting during chemotherapy, and
- to prevent or treat nausea and vomiting after surgery.

Geriatrics (65 years of age and older):

Ondansetron Omega is used to prevent nausea and vomiting during chemotherapy.

How does Ondansetron Omega work?

Ondansetron Omega is a medicine known as an antiemetic. Treatments such as cancer chemotherapy are associated with the release of a natural substance (serotonin). The release of serotonin, can make you feel sick and vomit. The way that Ondansetron Omega works is not known, but it is thought to help stop the effects of serotonin to reduce the effects of nausea and vomiting.

What are the ingredients in Ondansetron Omega?

Medicinal ingredient: ondansetron (as ondansetron hydrochloride dihydrate)

Non-medicinal ingredients: citric acid monohydrate, sodium chloride, sodium citrate, methylparaben*, propylparaben* (*present only in multidose vials).

Ondansetron Omega comes in the following dosage forms:
Solution for Injection: 2 mg/mL of ondansetron (as ondansetron hydrochloride dihydrate).

Do not use Ondansetron Omega, if:

- you are allergic to ondansetron hydrochloride dihydrate, or to any other ingredients in Ondansetron Omega.
- you are taking a medicine called apomorphine (used to treat Parkinson's disease).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Ondansetron Omega. Talk about any health conditions or problems you may have, including if you:

- have had an allergic reaction to medicines that are similar to Ondansetron Omega, such as medicines containing granisetron or palonosetron.
- are pregnant or planning to become pregnant. Ondansetron Omega is not recommended for use during pregnancy.
- are breast feeding or planning to breastfeed. Ondansetron Omega can pass into your breast milk and affect your baby have liver problems.
- have signs of intestinal obstruction or blockage.
- have or have had heart or blood vessel problems, including if you are at a higher risk for these problems. Risk factors include, but are not limited to, if you:
  - have family members who have or have had heart or blood vessel problems,
  - smoke,
  - have high blood pressure,
  - have high cholesterol levels,
  - have diabetes, or
  - are overweight.
- are taking medicines that affect the serotonin in your body (e.g., serotonergic and neuroleptic medications). If you are unsure, ask your healthcare professional.
- have QT/QTc prolongation (a heart rhythm condition) or a family history of QT/QTc prolongation.
- are taking medications that may lead to QT/QTc prolongation or electrolyte imbalances. If you are unsure, ask your healthcare professional.
- have low blood levels of potassium, magnesium, or calcium.

Other warnings you should know about:
Serotonin toxicity (also known as Serotonin syndrome): Ondansetron Omega can cause

serotonin toxicity, a rare but potentially life- threatening condition. It can cause serious changes in how your brain, muscles and digestive system work. You may develop serotonin toxicity if you take Ondansetron Omega with certain anti- depressants or migraine medications.

Serotonin syndrome symptoms include:

- fever, sweating, shivering, diarrhea, nausea, vomiting;
- muscle shakes, jerks, twitches or stiffness, overactive reflexes, loss of coordination;
- fast heartbeat, changes in blood pressure;
- confusion, agitation, restlessness, hallucinations, mood changes, unconsciousness, and coma.

Myocardial ischemia (lack of blood flow to the heart): Treatment with Ondansetron Omega can cause myocardial ischemia which can lead to a heart attack. This may happen shortly after Ondansetron Omega administration. Some symptoms of myocardial ischemia can include sudden chest pain, pressure or discomfort, feeling faint, feeling anxious, shortness of breath, irregular heartbeat, nausea, and sudden heavy sweating. Your healthcare professional will monitor your health during and after administration of Ondansetron Omega. However, if you notice any symptoms of myocardial ischemia, tell your healthcare professional right away. They may reduce or stop your treatment, and may recommend another therapy.

QT/QTc prolongation: Ondansetron Omega can affect the electrical activity of your heart known as QT/QTc prolongation. This effect can be measured with an electrocardiogram (ECG). In rare cases, QT/QTc prolongation can cause changes to the rhythm of your heart (e.g., fast, slow or irregular heartbeats). This can lead to dizziness, palpitations (sensation of rapid, pounding, or irregular heart beat), fainting, or death. You are at a higher risk if you have a heart disease, are taking certain interacting medicines, are a female, or are over the age of 65 years. It is important to follow the instructions of your healthcare professional with regard to dosing or any special tests. If you experience any symptoms of a possible heart rhythm problem, you should seek immediate medical attention.

Severe allergic reactions: Ondansetron Omega can cause allergic reactions in certain individuals. Symptoms of a severe allergic reaction can include wheezing, sudden chest pain, tightness of the chest, heart throbbing, swelling of eyelids, face or lips, or develop a skin rash, skin lumps or hives. If you notice any signs of a severe allergic reaction, **contact your healthcare professional immediately. Do not take any more medicine unless your healthcare professional tells you to do so.**

Pregnancy:

- If you are pregnant, there are specific risks for your unborn baby that you must discuss with your healthcare professional.
- If you are able to get pregnant, you may be asked to take a pregnancy test before starting your treatment with Ondansetron Omega.
- You should use effective birth control while you are taking Ondansetron Omega, and for at least 2 days after stopping Ondansetron Omega. Ask your healthcare professional about options of effective birth control.
- If you become pregnant while taking Ondansetron Omega, tell your healthcare professional right away.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Ondansetron Omega:

- medicines called CYP3A4 inducers (e.g., phenytoin, carbamazepine, and rifampicin);
- medicines used to treat heart rhythm disorders (e.g., quinidine, procainamide, disopyramide, amiodarone, sotalol, ibutilide, dronedarone, flecainide, and propafenone);
- medicines used to treat vomiting and nausea called antiemetics (e.g., dolasetron, palonosetron, granisetron, droperidol, chlorpromazine, prochlorperazine, and domperidone);
- medicines called tyrosine kinase inhibitors (e.g., vandetanib, sunitinib, nilotinib, and lapatinib);
- medicines used to manage psychosis or schizophrenia called antipsychotics (e.g., chlorpromazine, pimozide, haloperidol, and ziprasidone);
- medicines used to treat depression called antidepressants (e.g., citalopram, fluoxetine, venlafaxine, tricyclic/tetracyclic antidepressants, amitriptyline, imipramine, and maprotiline);
- medicines used to treat pain called opioids (e.g., methadone and tramadol);
- medicines used to treat bacterial infections called antibiotics (e.g., erythromycin, clarithromycin, telithromycin, tacrolimus, moxifloxacin, levofloxacin, and ciprofloxacin);
- medicines used to treat malaria called antimalarials (e.g., quinine and chloroquine);
- medicines used to treat fungal infections called azole antifungals (e.g., ketoconazole, fluconazole, and voriconazole);

- medicines used to treat cancer (e.g., vorinostat);
- medicines called beta-2 adrenoceptor agonists (e.g., salmeterol and formoterol);
- medicines that can affect electrolyte levels (e.g., diuretics, laxatives, enemas, amphotericin B, and high doses of corticosteroids);
- a medicine used to treat Parkinson's Disease called apomorphine;
- medicines called serotonergic drugs that can affect the serotonin in the body (e.g., triptans, Selective Serotonin-Reuptake Inhibitors (SSRIs), Serotonin Noradrenalin Reuptake Inhibitors (SNRIs), lithium, sibutramine, fentanyl and its analogues, dextromethorphan, tramadol, tapentadol, meperidine, methadone, pertazocine, St. John's Wort (Hypericum perforatum), monoamine oxidase inhibitors (MAOIs), linezolid, and methylene blue).

If you are unsure about any medications you are taking, ask your healthcare professional.

How to take Ondansetron Omega:

Ondansetron Omega will be prepared and administered by a healthcare professional or under the supervision of a healthcare professional.

Usual dose:
Your healthcare professional will determine the right dose and length of Ondansetron Omega for you. Your dose will depend on your medical condition, age, current health, and if you take certain other medications. Your healthcare professional may monitor your health throughout your treatment and may interrupt, reduce or stop your dose.

Ovedose:

If you think you, or a person you are caring for, have taken too much Ondansetron Omega, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

What are possible side effects from using Ondansetron Omega?

These are not all the possible side effects you may have when taking Ondansetron Omega. If you experience any side effects not listed here, tell your healthcare professional.

Some side effects may include:

- feeling of flushing or warmth;
- pain, redness, and burning at the site of injection;
- hiccups.

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

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
UNCOMMON			
Heart problems (disorders affecting your heart muscle, valves or rhythm): chest pain, chest discomfort, high blood pressure, irregular heart rhythm, shortness of breath, or fainting.			✓
Seizures: loss of consciousness with uncontrollable shaking visual disturbances (e.g., blurred vision).			✓
Movement disorders (including dyskinesia): loss of coordination or balance, speech or limb movements, muscle spasms, difficultly walking, tremor, upward rolling of the eyes, or abnormal muscular stiffness.			✓
RARE			
Eye problems such as blurred vision		✓	
Immediate severe allergic reaction: swelling of the mouth, throat, difficulty in breathing, rash, hives, or increased heart rate.			✓
Serotonin syndrome: a reaction which may cause feelings of agitation or restlessness, flushing, muscle twitching, involuntary eye movements, heavy sweating, high body temperature (> 38°C), or rigid muscles.			✓

Liver problems: yellowing of your skin and eyes (jaundice), unusual dark urine and pale stools, pain or swelling in the right upper abdomen, unusual tiredness, nausea, or vomiting.			✓
Hypokalemia (low level of potassium in the blood): muscle weakness, muscle spasms, cramping, constipation, feeling of skipped heart beats or palpitations, fatigue, tingling, or numbness			✓
Prolongation of QT interval (a heart rhythm condition): irregular heartbeat, palpitations, dizziness, fainting, loss of consciousness, or seizures.			✓
Hypotension (low blood pressure): dizziness, fainting, light-headedness, blurred vision, nausea, or vomiting.			✓
Myocardial ischemia (lack of blood flow to the heart which can lead to heart attack): sudden chest pain, pressure or discomfort, feeling faint, feeling anxious, shortness of breath, irregular heartbeat, nausea, or sudden heavy sweating.			✓
VERY RARE			
Eye problems such as temporary blindness		✓	
Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) (severe skin reactions): redness, blistering or peeling of the skin and/or inside of the lips, eyes, mouth, nasal passages or genitals, fever, chills, headache, cough, body aches, or swollen glands.			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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

Storage:

Ondansetron Omega should be stored between 15 °C and 30°C. Do not freeze. Protect from light.

Keep your medicine in a safe place out of reach and sight of children. Your medicine may harm them.

If you want more information about Ondansetron Omega:

- Talk to your healthcare professional.
- Find the full Product Monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug- products/drug-product-database.html); the manufacturer's website https://www.omegapharma.ca/ or by calling 1-800-363-0584.

This leaflet was prepared by Omega Laboratories Limited

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