PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrZOFRAN®

ondansetron hydrochloride dihydrate

Tablets, 4 mg and 8 mg, oral

Oral solution, 4 mg/5 mL, oral

Injection, 2 mg/mL, intravenous

PrZOFRAN® ODT

ondansetron

Orally disintegrating tablets, 4 mg and 8 mg, oral

Antiemetic

5-HT3 receptor antagonist

ATC code A04AA01

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RECENT MAJOR LABEL CHANGES

7 WARNING AND PRECAUTIONS, Cardiovascular, Myocardial Ischemia and Coronary Artery Spasm	11/2021
7 WARNING AND PRECAUTIONS, Special Populations, 7.1.1 Pregnant Women	10/2020

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Adults (18-64 years of age)
ZOFRAN® (ondansetron hydrochloride dihydrate; and ondansetron) is indicated for:

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

1.1 Pediatrics (<18 years of age)

Post-Chemotherapy Induced Nausea and Vomiting

- **Pediatrics (4-12 years of age):** ZOFRAN was effective and well tolerated when given to children 4-12 years of age
- **Pediatrics (<4 years of age):** ZOFRAN is not indicated for the treatment of children less than 4 years old.

Post-Radiotherapy Induced Nausea and Vomiting
ZOFRAN is not indicated for this use in any pediatric population.

Post-Operative Nausea and Vomiting
ZOFRAN is not indicated for this use in any pediatric population.

1.2 Geriatrics (≥65 years of age)

Post-Chemotherapy and Radiotherapy Induced Nausea and Vomiting
Efficacy and tolerance of ZOFRAN 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.

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

2 CONTRAINDICATIONS

- ZOFRAN (ondansetron hydrochloride; and ondansetron) is contraindicated in patients with a history of hypersensitivity to the drug or any components of its formulations. 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.

ZOFRAN 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 or oral dose. See 7 WARNINGS AND PRECAUTIONS, Hepatic.

ZOFRAN 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 ZOFRAN 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:

- Use the minimum effective dose.
- Use oral formulations if possible (lower Cmax).

- Intravenous dosing considerations:
    - **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 ZOFRAN 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.

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

4.2 Recommended Dose and Dosage Adjustment

Highly Emetogenic Chemotherapy Induced Nausea and Vomiting

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

- ***Use in Adults (only)***
  - Initial IV dose, diluted (see 4.4 Administration), infused over 15 minutes, given 30 minutes before chemotherapy:
    - usually 8 mg
    - maximum 16 mg.
  - Post-chemotherapy:
    - 4 hours and 8 hours after the initial dose: 8 mg IV, infused over 15 minutes.
    - After the first 24 hours: 8 mg orally every 8 hours, for up to 5 days.

Less Emetogenic Chemotherapy Induced Nausea and Vomiting

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

- ***Use in Adults:***
  - Initial dose:
    - 8 mg orally, given 1-2 hours before chemotherapy.

      OR
    - 8 mg IV, diluted (see 4.4 Administration), infused over 15 minutes, given 30 minutes before chemotherapy.
  - After chemotherapy: doses of 8 mg orally, twice daily, for up to 5 days.

- ***Use in Children 4-12 years of age***

- Initial dose: 3 to 5 mg/m2 IV, infused over 15 minutes, at least 30 minutes before chemotherapy.
- After chemotherapy: 4 mg orally, every 8 hours.

- ***Use in Children <4 years of age***
  ZOFRAN is not indicated for this use in this pediatric population.

- ***Use in Elderly (<=65 years of age):***
  See 4.4 Administration; 10.3 Pharmacokinetics, Geriatrics.

Elderly (65-74 years of age):

- Initial IV dose: 8 mg or 16* mg, diluted, infused over 15 minutes.
- 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 QTcF interval prolongation above 10 ms (from baseline) for about 10 min. ECG monitoring may be considered.

Elderly (>=75 years of age):

- Initial IV dose: maximum 8 mg, diluted, infused over 15 minutes.
- May be followed by two IV doses** of 8 mg, diluted, 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 interval prolongation above 10 ms (from baseline) for about 10 min. ECG monitoring may be considered.

Radiotherapy Induced Nausea and Vomiting
Caution: To reduce cardiac risks, carefully follow the dosing guidelines under 4.1 Dosing Considerations.

- ***Use in Adults:***
  - Initial dose: 8 mg orally, given 1 to 2 hours before radiotherapy.
  - After radiotherapy: 8 mg orally, given every 8 hours, for up to 5 days after a course of treatment.

- ***Use in Children (<18 years of age):***
  ZOFRAN is not indicated for this use in the pediatric population.

- ***Use in Elderly (<=65 years of age):***
  See Use in Adults, and 4.1 Dosing Considerations; 10.3 Pharmacokinetics, Geriatrics.

Post-Operative Nausea and Vomiting

- ***Use in Adults:***
  - For prevention:
    - One hour prior to anaesthesia: 16 mg orally.

      OR
    - At induction of anaesthesia: 4 mg IV, undiluted, infused - preferably over 2-5 minutes, and not less than 30 seconds.
  - For established post-operative nausea and vomiting:
    - A single dose of 4 mg IV, infused - preferably over 2-5 minutes, and not less than 30 seconds.

- ***Use in Children (<18 years of age):***

  ZOFRAN is not indicated for this use in the pediatric population.

- ***Use in Elderly (<=65 years of age):***

  ZOFRAN is not indicated for this use in the elderly.

4.4 Administration

Administration of Tablets

ZOFRAN tablets should be swallowed whole, with a liquid.

Administration of Orally Dispersible Tablets

Patient instructions:

- **Do not** try to push ZOFRAN ODT out through the foil backing on the blister pocket.
- Just prior to use, with dry fingers, carefully peel back the foil backing where indicated by the arrow. Gently push the tablet out of the blister pocket.
- Immediately place the ZOFRAN ODT tablet on top of the tongue. It will disperse within seconds, then swallow as normal.

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:***

ZOFRAN Injection should only be mixed with the infusion solutions recommended below:

0.9% w/v Sodium Chloride Injection;

5% w/v Dextrose Injection;

10% w/v Mannitol Injection;

Ringers Injection;

0.3% w/v Potassium Chloride and 0.9% w/v Sodium Chloride Injection;

0.3% w/v Potassium Chloride and 5% w/v Dextrose Injection.

- ***Compatibility with Other Drugs:***

ZOFRAN Injection should not be administered in the same syringe or infusion with any other medication with the exception of dexamethasone (see below).

The following drugs may be administered via the Y-site of the administration set, for ondansetron concentrations of 16 to 160 mcg/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.
- **Dexamethasone** - admixtures containing 8 mg of ondansetron and 20 mg of dexamethasone phosphate, in 50 mL of 5% dextrose infusion fluid stored in 50 mL polyvinyl chloride infusion bags, have been shown to be physically and chemically stable for up to two days at room temperature or up to seven days at 2 – 8 ºC. In addition, these same admixtures have demonstrated compatibility with Continu-Flo administration sets.
- **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 - 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 - 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 paediatric 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	Non-medicinal Ingredients
Oral	Tablets/	lactose, magnesium stearate, methyl

	4 mg and 8 mg ondansetron base (as hydrochloride dihydrate)	hydroxypropyl cellulose, microcrystalline cellulose, Opadry yellow or Opaspray yellow (containing titanium dioxide and iron oxide yellow) and pregelatinised starch.
Oral	Oral solution/ 4 mg/5 mL ondansetron base (as hydrochloride dihydrate)	citric acid, sodium benzoate, sodium citrate dihydrate, sorbitol, strawberry flavour (contains ethanol).
Oral	ODT Orally disintegrating tablets/ 4 mg and 8 mg ondansetron (base)	aspartame, gelatine, mannitol, sodium methyl hydroxybenzoate, sodium propyl hydroxybenzoate, and strawberry flavour (contains ethanol).
Intravenous	Injection/ 2 mg/mL ondansetron base (as hydrochloride dihydrate)	2 mL or 4 mL ampoules: citric acid monohydrate, sodium chloride, sodium citrate.

Description

ZOFRAN Tablets 4 mg:

Oval shaped, yellow, film-coated tablets, engraved 'GX ET3'. Each tablet contains 4 mg ondansetron base (as hydrochloride dihydrate) and the following excepients: lactose, microcrystalline cellulose, pregelatinised starch, magnesium stearate and methyl hydroxypropyl cellulose and the colouring agents Opadry yellow or Opaspray yellow (containing titanium dioxide and iron oxide yellow).

Available in a unit dosed blister pack of 10 tablets.

ZOFRAN Tablets 8 mg:

Oval shaped, yellow, film-coated tablets, engraved 'GX ET5'. Each tablet contains 8 mg ondansetron base (as hydrochloride dihydrate) and the following excepients: lactose, microcrystalline cellulose, pregelatinised starch, magnesium stearate and methyl hydroxypropyl cellulose and the colouring agents Opadry yellow or Opaspray yellow (containing titanium dioxide and iron oxide yellow).

Available in a unit dosed blister pack of 10 tablets.

ZOFRAN Oral Solution:

ZOFRAN Oral Solution contains 4 mg/5 mL of ondansetron base in the form of ondansetron hydrochloride dihydrate. ZOFRAN Oral Solution also contains the following excipients: citric acid, sodium citrate dihydrate, sodium benzoate and strawberry flavour (contains ethanol). ZOFRAN Oral Solution is sucrose-free and is sweetened with sorbitol.

Ondansetron 4 mg/5 mL (as hydrochloride dihydrate) is supplied in 50 mL bottles.

ZOFRAN ODT 4 mg and 8 mg orally disintegrating tablets:

White, round, plano-convex orally disintegrating tablets with no markings on either side. Each 4 mg tablet contains 4 mg ondansetron (base) and each 8 mg tablet contains 8 mg ondansetron (base). ODT orally disintegrating tablets also contain gelatine, mannitol, aspartame, strawberry flavour (contains ethanol), and sodium methyl hydroxybenzoate and sodium propyl hydroxybenzoate.

ZOFRAN ODT orally disintegrating tablets are packaged in double-foil blister packs with a peelable, aluminum foil laminate lidding, in paperboard carton with 2 x 5 orally disintegrating tablets per blister.

ZOFRAN Injection:

ZOFRAN Injection contains 2 mg/mL of ondansetron base, in the form of ondansetron hydrochloride dihydrate.

ZOFRAN Injection (2 mL and 4 mL ampoules) also contains:

citric acid monohydrate	0.50 mg/mL
sodium citrate	0.25 mg/mL
sodium chloride	9.00 mg/mL

Ondansetron 2 mg/mL (as hydrochloride dihydrate) for intravenous use is supplied in 2 mL (4 mg) and 4 mL (8 mg) ampoules, in boxes of 5 ampoules.

7 WARNINGS AND PRECAUTIONS

General

ZOFRAN ODT (ondansetron) contains aspartame and therefore should be taken with caution in patients with phenylketonuria.

ZOFRAN (ondansetron hydrochloride; and ondansetron) 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.

Hypokalaemia, hypocalcaemia and hypomagnesemia should be corrected prior to ondansetron administration.

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

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

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

Neurologic
Serotonin syndrome/Neuroleptic Malignant Syndrome: Cases of life-threatening serotonin syndrome or neuroleptic malignant syndrome-like events have been reported with 5-HT3 receptor antagonist antiemetics, including ZOFRAN and ZOFRAN ODT, when given in combination with other serotonergic and/or neuroleptic drugs. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhoea). As these syndromes may result in potentially life-threatening conditions, treatment should be discontinued if such events occur and supportive symptomatic treatment should be initiated. If concomitant treatment of ZOFRAN or ZOFRAN ODT with a drug affecting the serotonergic neurotransmitter system is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see 9 DRUG INTERACTIONS).

Reproductive Health: Female and Male Potential

Pregnancy status should be verified for females of reproductive potential prior to starting the treatment with ZOFRAN or ZOFRAN ODT.

Females of reproductive potential should be advised that it is possible that ZOFRAN/ZOFRAN ODT can cause harm 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 ZOFRAN or ZOFRAN ODT and for two days after stopping treatment with ZOFRAN or ZOFRAN ODT.

7.1 Special Populations

7.1.1 Pregnant Women

The use of ondansetron in 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 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, nursing is not recommended during treatment with ondansetron.

7.1.3 Pediatrics

Insufficient information is available to provide dosage recommendations for children 3 years of age or younger.

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 Trial 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.

ZOFRAN (ondansetron hydrochloride; and 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.

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

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 hypokalaemia.

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

8.5 Post-Market Adverse Reactions

Over 250 million patient treatment days of ZOFRAN have been supplied since the launch of the product worldwide. The following events have been spontaneously reported during post-

approval use of ZOFRAN, 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 oedema, 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 IV infusion of ondansetron.

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

Serotonin syndrome and neuroleptic malignant syndrome-like events have been reported with 5-HT_3 receptor antagonist antiemetics, including ZOFRAN and ZOFRAN ODT, 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.

9.4 Drug-Drug Interactions

CYP 3A4 inducers: Despite the multiplicity of metabolic enzymes capable of metabolising ondansetron, which might be expected to compensate for an increase or decrease in enzyme activity, 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.

In a pharmacokinetic study of 16 epileptic patients maintained chronically on carbamazepine or phenytoin (CYP 3A4 inducers), reduction in AUC, Cmax and T½ of ondansetron was observed. This resulted in a significant increase in clearance. However, on the basis of the inter-subject variability in the available data, no dosage adjustment can be recommended.

CYP 2D6 inhibitors: No effect in ondansetron clearance secondary to enzyme inhibition has been identified to date.

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

- Class IA antiarrhythmics (e.g., quinidine, procainamide, disopyramide);
- Class III antiarrhythmics (e.g., amiodarone, sotalol, ibutilide, dronedarone);
- Class 1C antiarrhythmics (e.g., flecainide, propafenone);
- antiemetics (e.g., dolasetron, 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 antidepressants e.g., amitriptyline, imipramine, maprotiline);
- opioids (e.g., methadone);
- domperidone;
- macrolide antibiotics and analogues (e.g., erythromycin, clarithromycin, telithromycin, tacrolimus);
- quinolone antibiotics (e.g., moxifloxacin, levofloxacin, ciprofloxacin);
- antimalarials (e.g., quinine, chloroquine);
- azole antifungals (e.g., ketoconazole, fluconazole, voriconazole);
- histone deacetylase inhibitors (e.g., vorinostat);
- beta-2 adrenoceptor agonists (e.g., salmeterol, formoterol).

Drugs that Cause Electrolyte Abnormalities: The use of ZOFRAN 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.

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

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

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

Serotonergic Drugs: As with other serotonergic agents, serotonin syndrome, a potentially life-threatening condition, may occur with 5-HT_3 receptor antagonist antiemetic treatment when given in combination with other agents that may affect the serotonergic neurotransmitter system [including triptans, SSRIs, SNRIs, lithium, sibutramine, fentanyl and its analogues, dextromethorphan, tramadol, tapentadol, meperidine, methadone and pertazocine or St. John's Wort (*Hypericum perforatum*)] and with drugs which impair metabolism of serotonin (such as MAOIs, including linezolid (an antibiotic which is a reversible non-selective MAOI) and methylene blue) (see 7 WARNINGS AND PRECAUTIONS, Neurologic).

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with food have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with food have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

ZOFRAN (ondansetron hydrochloride; and ondansetron) is a selective antagonist of the serotonin receptor subtype, 5-HT_3. Its precise mode of action in the control of chemotherapy induced nausea and vomiting is not known.

Cytotoxic chemotherapy and radiotherapy are associated with the release of serotonin (5-HT) from enterochromaffin cells of the small intestine, presumably initiating a vomiting reflex through stimulation of 5-HT_3 receptors located on vagal afferents. Ondansetron may block the initiation of this reflex. Activation of vagal afferents may also cause a central release of serotonin from the chemoreceptor trigger zone of the area postrema, located on the floor of the fourth ventricle. Thus, the antiemetic effect of ondansetron is probably due to the selective antagonism of 5-HT_3 receptors on neurons located in either the peripheral or central nervous systems, or both.

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

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.

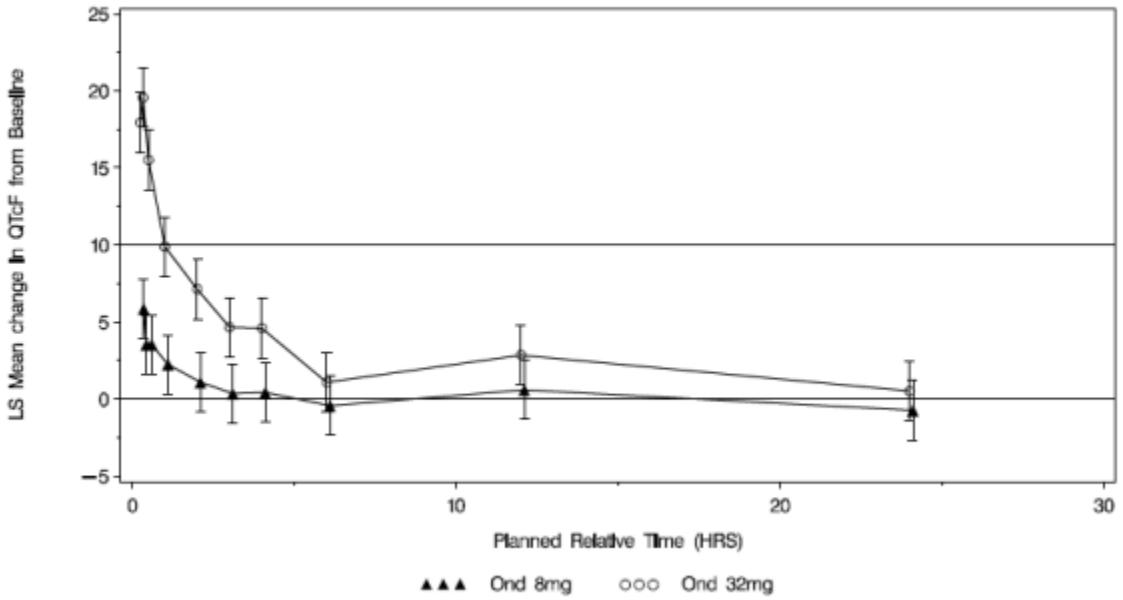
Intravenous infusion of either 1 mg or 5 mg ondansetron tended to increase small bowel transit times and single intravenous doses of 10 mg ondansetron have been reported to decrease sphincter pressure in the lower oesophagus in some subjects.

Electrocardiography

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 ZOFRAN. On the basis of pharmacokinetic-pharmacodynamic modelling, an 8 mg oral dose of ZOFRAN is predicted to cause a mean QTcF increase of 0.7 ms (90% CI -2.1, 3.3) at steady-state, assuming a mean maximal plasma concentration of 24.7 ng/mL (95% CI 21.1, 29.0).

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

10.3 Pharmacokinetics

Absorption

- Oral administration

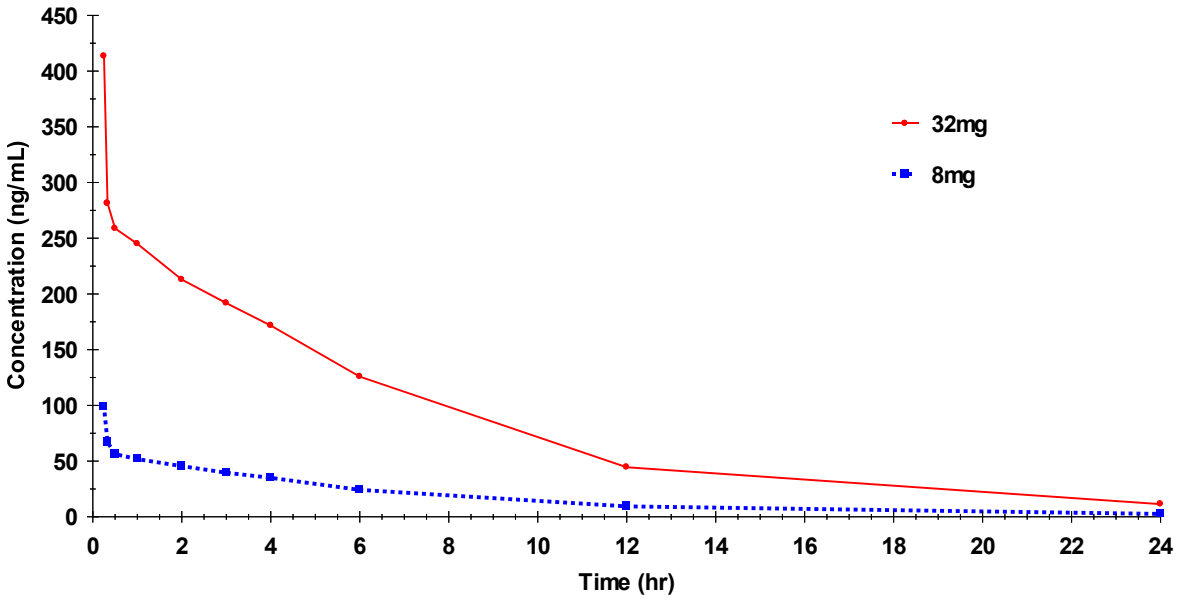
Pharmacokinetic studies in human volunteers showed peak plasma levels of 20-30 ng/mL at around 1½ hours after an 8 mg oral dose of ondansetron. Repeat dosing of an 8 mg tablet every 8 hours for 6 days increased the peak plasma value to 40 ng/mL.

- Intravenous administration

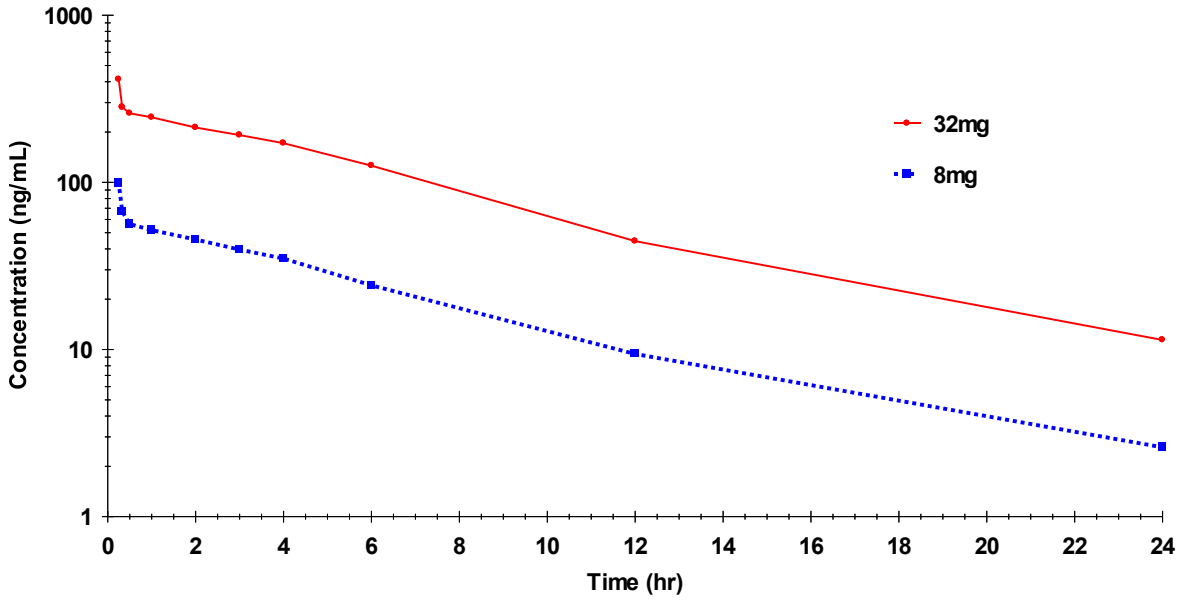
Pharmacokinetic studies in human volunteers: An 8 mg infusion of ondansetron resulted in peak plasma levels of 80-100 ng/mL. A continuous intravenous infusion of 1 mg/hour after the initial 8 mg loading dose of ondansetron maintained plasma levels over 30 ng/mL during the following 24-hour period.

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%), sulphate conjugates (20%) and hydroxylation products (10%).

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

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)

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**

The clearance of an 8 mg intravenous dose of ZOFRAN was significantly reduced and the serum half-life significantly prolonged in subjects with severe impairment of hepatic function. In patients with moderate or severe impairment of hepatic function, reductions in dosage are therefore recommended and a total daily dose of 8 mg should not be exceeded. This may be given as a single intravenous or oral dose.
There is no experience in patients who are clinically jaundiced.

- **Renal Insufficiency**

No alteration of daily dosage, frequency of dosing, or route of administration is required in patients with impaired renal function.

11 STORAGE, STABILITY AND DISPOSAL

ZOFRAN (ondansetron hydrochloride; and ondansetron) Tablets, Oral Solution, Injection and ODT orally disintegrating tablets should be stored below 30°C.

ZOFRAN Oral Solution should be stored upright between 15°C and 30°C and should not be refrigerated.

ZOFRAN Injection should not be frozen and should be protected from light. ZOFRAN Injection must not be autoclaved. Store below 30°C.

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

There is no specific instruction for disposal.

12 SPECIAL HANDLING INSTRUCTIONS

Ampoule Opening Instructions for ZOFRAN Injection (2 mL and 4 mL ampoules)

Ampoules are equipped with One Point Cut opening system and must be opened using the following instructions:

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

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

Picture 1

Picture 2

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: ondansetron hydrochloride dihydrate (for tablets and injection)

ondansetron (for orally disintegrating tablets)

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

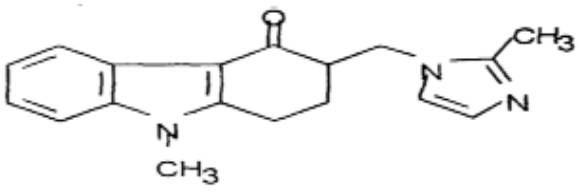
*Salt used in tablets and injection. Ondansetron (base) is used in ODT orally disintegrating tablets.

Molecular formula and molecular mass:

C18H19N3O.HCl.2H2O (hydrochloride dihydrate), 365.9 (hydrochloride hydrate)

C18H19N3O (base), 293.4 (base)

Structural formula:



- $HCl.\ 2H_2O$

Physicochemical properties:

Description and Solubility:

- **Hydrochloride dihydrate**

  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

- **Base**

  Ondansetron is a white to off-white powder. It is soluble at pH 1.2. Practically insoluble in water. Solubility decreases with increasing pH from very slightly soluble at pH 3.5 and pH 5.4 to practically insoluble at pH 8. Soluble in chloroform and slightly soluble in acetonitrile and methanol.

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	ZOFRAN* 3 doses of 0.15 mg/kg	Placebo* 3 doses of placebo	ZOFRAN 8 mg IV + 1 mg/hr, 24 hours	ZOFRAN 8 mg IV	ZOFRAN 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.

Table 3: Prevention of Post-Operative Emesis – Response Over 24 Hours*

	Oral Prevention			**Intravenous Prevention**		
Dose	ZOFRAN 16 mg od	Placebo	*p value*	ZOFRAN 4 mg IV	Placebo	*p value*
# of patients	253	250		136	139	

Treatment Response: 0 emetic episodes	126 (50%)	79 (32%)	< 0.001	103 (76%)	62 (46%)	< 0.001

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

Table 4: Treatment of Post-Operative Emesis – Response Over 24 Hours*			
Intravenous Treatment			
Dose	ZOFRAN 4 mg IV	Placebo	*p value*
# of patients	104	117	
Treatment Response: 0 emetic episodes	49 (47%)	19 (16%)	< 0.001

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

Table 5: Prevention of Radiotherapy Induced Emesis – Response Over 24 Hours*			
Oral Treatment			
Dose	ZOFRAN 8 mg PO tid*	Metoclopramide 10 mg PO tid*	*p value*
# of patients	38	44	
Treatment Response: 0 emetic episodes	37 (97%)	20 (45%)	< 0.001

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

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

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.

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

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 IV dose and 8 to 15 ng/mL for the oral dose. Plasma levels were linear over a 30-fold dose range. In repeat-dose studies there was no apparent accumulation of ondansetron.

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

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

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 6

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**

Table 7 - Subacute Toxicity Studies

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

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

Table 8 - Chronic Toxicity

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

Carcinogenicity

Table 9 - 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 foetal and post-natal development were detected in rats and no foetal abnormalities were observed in rabbits after oral administration of ondansetron.

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

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

Daily administration of ondansetron at dosages up to 15 mg/kg/day to pregnant rats (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. Foetal development of the F2 generation was comparable to controls; however, the number of implantations and viable foetuses was reduced in the highest dosage group when compared with controls.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrZOFRAN® (Tablets and Oral Solution)

ondansetron hydrochloride dihydrate tablets, and

ondansetron hydrochloride dihydrate oral solution

PrZOFRAN® ODT (Orally Disintegrating Tablets)

ondansetron orally disintegrating tablets

Read this carefully before you start taking **ZOFRAN and ZOFRAN ODT** 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 **ZOFRAN and ZOFRAN ODT**.

What is ZOFRAN and ZOFRAN ODT used for?

Children (4 to 17 years of age):

ZOFRAN (ondansetron hydrochloride dihydrate) and ZOFRAN ODT (ondansetron) are used to prevent nausea and vomiting during chemotherapy.

Adults (18 to 64 years of age):

ZOFRAN and ZOFRAN ODT are used:

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

Geriatrics (65 years of age and older):

ZOFRAN and ZOFRAN ODT are used to prevent nausea and vomiting during chemotherapy and radiotherapy.

How does ZOFRAN and ZOFRAN ODT work?

ZOFRAN and ZOFRAN ODT are medications known as antiemetics. Treatments such as cancer chemotherapy and radiotherapy are associated with the release of a natural substance (serotonin). The release of serotonin, can make you feel sick and vomit. The way that ZOFRAN and ZOFRAN ODT work 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 ZOFRAN and ZOFRAN ODT?

ZOFRAN (Tablets)

- Medicinal ingredient: ondansetron hydrochloride dihydrate.
- Non-medicinal ingredients: lactose, magnesium stearate, methyl hydroxypropyl cellulose, microcrystalline cellulose, Opaspray or Opadry yellow (containing titanium dioxide and iron oxide yellow), and pregelatinized starch.

ZOFRAN (Oral Solution)

- Medicinal ingredient: ondansetron hydrochloride dihydrate.
- Non-medicinal ingredients: citric acid, sodium benzoate, sodium citrate dihydrate, sorbitol, and strawberry flavour (contains ethanol (alcohol)).

ZOFRAN ODT (Orally Disintegrating Tablets)

- Medicinal ingredient: ondansetron.
- Non-medicinal ingredients: aspartame, gelatine, mannitol, sodium methyl hydroxybenzoate, sodium propyl hydroxybenzoate, and strawberry flavour (contains ethanol (alcohol)).

ZOFRAN and ZOFRAN ODT comes in the following dosage forms:

ZOFRAN:

- Tablets: 4 mg and 8 mg of ondansetron (as ondansetron hydrochloride dihydrate).
- Oral Solution: 4 mg / 5 mL of ondansetron (as ondansetron hydrochloride dihydrate).

ZOFRAN ODT:

- Orally disintegrating tablets: 4 mg and 8 mg of ondansetron.

Do not use ZOFRAN or ZOFRAN ODT if:

- you are allergic to ondansetron or ondansetron hydrochloride dihydrate, or to any other ingredients in ZOFRAN or ZOFRAN ODT.
- 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 ZOFRAN or ZOFRAN ODT. Talk about any health conditions or problems you may have, including if you:

- have had an allergic reaction to medicines that are similar to ZOFRAN and ZOFRAN ODT such as medicines containing granisetron or palonosetron.
- are pregnant or planning to become pregnant. ZOFRAN and ZOFRAN ODT are not recommended for use during pregnancy.
- are breast-feeding or planning to breastfeed. ZOFRAN and ZOFRAN ODT 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.
- have a condition called phenylketonuria, as ZOFRAN ODT contains aspartame.
- are taking medications 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 syndrome: ZOFRAN and ZOFRAN ODT can cause serotonin syndrome, 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 syndrome if you take ZOFRAN or ZOFRAN ODT 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 ZOFRAN and ZOFRAN ODT can cause myocardial ischemia which can lead to a heart attack. This may happen shortly after ZOFRAN or ZOFRAN ODT 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 ZOFRAN or ZOFRAN ODT. 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: ZOFRAN and ZOFRAN ODT 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: ZOFRAN and ZOFRAN ODT 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 ZOFRAN or ZOFRAN ODT.
- You should use effective birth control while you are taking ZOFRAN or ZOFRAN ODT, and for at least 2 days after stopping ZOFRAN or ZOFRAN ODT. Ask your healthcare professional about options of effective birth control.
- If you become pregnant while taking ZOFRAN or ZOFRAN ODT, 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 ZOFRAN or ZOFRAN ODT:

- 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 ZOFRAN or ZOFRAN ODT:

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

For ZOFRAN tablets:

- ZOFRAN tablets should be swallowed whole with a liquid.

For ZOFRAN ODT orally disintegrating tablets:

- Do not try to push or force ZOFRAN ODT out through the foil package without first peeling the foil back. To take ZOFRAN ODT out of the foil package, tear along the perforations (dotted lines) to separate one tablet in its blister unit from the rest of the package. Just before you need to take it, with dry fingers, carefully peel back the foil at the place indicated by the arrow, and gently push the ZOFRAN ODT tablet out of the blister pocket.
- To take the ZOFRAN ODT, promptly place it on top of your tongue, let it dissolve, and then swallow. It will dissolve very quickly.

Usual dose:

Take ZOFRAN or ZOFRAN ODT exactly as your healthcare professional has told you. Your healthcare professional will determine the right dose and length of ZOFRAN or ZOFRAN ODT 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.

Overdose:

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

Missed Dose:

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

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

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

What are possible side effects from using ZOFRAN or ZOFRAN ODT?

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

Some side effects may include:

- feeling of flushing or warmth;
- hiccups.

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

If you feel unwell or have any symptoms that you do not understand, you should contact 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,			✓

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**	
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.			✓

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**	
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 healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

ZOFRAN tablets should be stored below 30°C.

ZOFRAN oral solution should be stored in its bottle, upright, between 15°C and 30°C. Do not refrigerate.

ZOFRAN ODT orally disintegrating tablets should be stored below 30°C.

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 ZOFRAN or ZOFRAN ODT:

- 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 http://www.novartis.ca, or by calling 1-800-363-8883.

This leaflet was prepared by Novartis Pharmaceuticals Canada Inc.

Last Revised November 9, 2021

ZOFRAN is a registered trademark

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]ZOFRAN® (Solution for Injection)

ondansetron hydrochloride dihydrate solution for injection

Read this carefully before you start taking **ZOFRAN** 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 **ZOFRAN.**

What is ZOFRAN used for?

Children (4 to 17 years of age):

ZOFRAN (ondansetron hydrochloride dihydrate) is used to prevent nausea and vomiting during chemotherapy.

Adults (18 to 64 years of age):

ZOFRAN is used:

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

Geriatrics (65 years of age and older):

ZOFRAN is used to prevent nausea and vomiting during chemotherapy and radiotherapy.

How does ZOFRAN work?

ZOFRAN is a medicine known as an antiemetic. Treatments such as cancer chemotherapy and radiotherapy are associated with the release of a natural substance (serotonin). The release of serotonin, can make you feel sick and vomit. The way that ZOFRAN 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 ZOFRAN?

Medicinal ingredient: ondansetron hydrochloride dihydrate

Non-medicinal ingredients: citric acid monohydrate, sodium chloride, and sodium citrate.

ZOFRAN comes in the following dosage forms:

Solution for Injection: 2 mg/mL of ondansetron (as ondansetron hydrochloride dihydrate).

Do not use ZOFRAN, if:

- you are allergic to ondansetron hydrochloride dihydrate, or to any other ingredients in ZOFRAN.
- 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 ZOFRAN. Talk about any health conditions or problems you may have, including if you:

- have had an allergic reaction to medicines that are similar to ZOFRAN, such as medicines containing granisetron or palonosetron.
- are pregnant or planning to become pregnant. ZOFRAN is not recommended for use during pregnancy.
- are breast-feeding or planning to breastfeed. ZOFRAN 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 syndrome: ZOFRAN can cause serotonin syndrome, 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 syndrome if you take ZOFRAN 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 ZOFRAN can cause myocardial ischemia which can lead to a heart attack. This may happen shortly after ZOFRAN 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 ZOFRAN. 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: ZOFRAN 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: ZOFRAN 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 ZOFRAN.
- You should use effective birth control while you are taking ZOFRAN, and for at least 2 days after stopping ZOFRAN. Ask your healthcare professional about options of effective birth control.

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 ZOFRAN:

- 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 ZOFRAN:

ZOFRAN injection 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 ZOFRAN 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.

Overdose:

If you think you, or a person you are caring for, have taken too much ZOFRAN, 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 ZOFRAN?

These are not all the possible side effects you may have when taking ZOFRAN. 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).			✓

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**	
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):			✓

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**	
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 healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

ZOFRAN injection (unopened ampoule) should be stored below 30°C. Do not freeze or autoclave. 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 ZOFRAN:

- 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 http://www.novartis.ca, or by calling 1-800-363-8883.

This leaflet was prepared by Novartis Pharmaceuticals Canada Inc.

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