AUSTRALIAN PRODUCT INFORMATION
ZOFRAN (Ondansetron hydrochloride dihydrate) injections, tablets and oral liquid, ZOFRAN (Ondansetron) suppositories and ZOFRAN ZYDIS (Ondansetron) wafers

1 NAME OF THE MEDICINE

Ondansetron hydrochloride dihydrate is the therapeutically active ingredient in Zofran injections, Zofran tablets and Zofran oral liquid.

Ondansetron is the therapeutically active ingredient in Zofran suppositories and in Zofran Zydis wafers.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Zofran 4 mg and 8 mg tablets contain 4 and 8 mg of ondansetron (as ondansetron hydrochloride dihydrate) and the following excipients: lactose monohydrate, microcrystalline cellulose, pregelatinised maize starch, magnesium stearate, hypromellose, titanium dioxide and iron oxide yellow.

Excipients with known effect: sugars as lactose

Zofran 24 mg tablets contain 24 mg of ondansetron (as ondansetron hydrochloride dihydrate) and the following excipients: lactose, microcrystalline cellulose, pregelatinised maize starch, magnesium stearate and Opadry Pink YS-1-14593-A (ARTG PI No: 3522).

Excipients with known effect: sugars as lactose

Zofran oral liquid contains 0.8 mg/mL of ondansetron (as ondansetron hydrochloride dihydrate) and the following excipients: citric acid, sodium citrate dihydrate, sodium benzoate, sorbitol solution (70 percent) (crystallising), purified water and Strawberry Flavouring Liquid SC887891 (ARTG PI No: 140281).

Excipients with known effect: benzoates and sorbitol (12.6g per recommended maximum daily dose) which may have a laxative effect or cause diarrhoea

Zofran Zydis wafers contain 4 and 8 mg of ondansetron and the following excipients: gelatin, mannitol, aspartame, sodium methyl hydroxybenzoate, sodium propyl hydroxybenzoate and Strawberry Flavouring Liquid SC887891 (ARTG PI No: 140281).

Excipients with known effect: aspartame, hydroxybenzoates and sulphites.

Each 2 mL Zofran injection contains 4 mg of ondansetron (as ondansetron hydrochloride dihydrate) and the following excipients: citric acid monohydrate, sodium citrate dihydrate, sodium chloride and water for injections.

Each 4 mL Zofran injection contains 8 mg of ondansetron (as ondansetron hydrochloride dihydrate) and the following excipients: citric acid monohydrate, sodium citrate dihydrate, sodium chloride and water for injections.

Zofran suppositories contain 16 mg of ondansetron and Witepsol (ARTG PI No: 2850).

3 PHARMACEUTICAL FORM

Zofran 4 mg tablet
Yellow, oval, bi-convex tablets, engraved with “GXET3” on one face and plain on the other face.

Zofran 8 mg tablet
Yellow, oval, bi-convex tablets, engraved with “GXET5” on one face and plain on the other face.

Zofran oral liquid
A clear, colourless to light yellow liquid.

Zofran Zydis wafer
White, round and plano-convex, no markings on either side.
‘Wafer’ is used to describe the pharmaceutical dosage form of Zofran Zydis.

Zofran 24 mg tablet*
Pink, oval, bi-convex tablets engraved 'GX CF7' on one face and '24' on the other

Zofran suppository *
White, smooth homogenous suppository with a torpedo shape.

Zofran Injection*
Clear colourless liquid, practically free of particles.

*****Not marketed in Australia

4.CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Ondansetron (tablets, oral liquid, wafers, suppository and injection) is indicated for the prevention and treatment of nausea and vomiting induced by cytotoxic therapy and radiotherapy. Ondansetron (injection) is also indicated for the prevention and treatment of post-operative nausea and vomiting.

4.2 DOSE AND METHOD OF ADMINISTRATION

The emetogenic potential of cancer treatment varies according to the doses and combinations of chemotherapy and radiotherapy regimens used. The route of administration and dose of Zofran should be flexible in the range of 8-32 mg a day and selected as shown below. The lowest effective dose should be used.

Zofran Zydis wafers: The Zofran Zydis wafer is administered by placing on top of the tongue where it dissolves within seconds, and is swallowed.

ADULTS

Emetogenic chemotherapy and radiotherapy (injection, tablets, suppositories, wafers, or oral liquid)
For the control of chemotherapy or radiotherapy induced emesis or nausea in adults, a single dose of 8 mg of ondansetron should be administered as a slow intravenous injection in not less than 30 seconds, immediately before treatment. Alternatively, two oral doses of 8 mg each at **12 hourly intervals** may be given (tablets, oral liquid or wafers), the first dose being administered 2 hours prior to chemotherapy or radiotherapy, or a single ondansetron 16 mg suppository, 2 hours before treatment.

To protect against delayed emesis after the first 24 hours, ondansetron should be continued orally at a dosage of 8 mg **twice daily**, or given rectally as a 16 mg suppository once daily, for up to 5 days after a course of treatment.

Highly emetogenic chemotherapy
A single dose of ondansetron 8 mg by slow intravenous injection in not less than 30 seconds, immediately before chemotherapy has been shown to be effective in many patients. Higher doses may be required in some patients, particularly those on high dose cisplatin, and the doses should be adjusted according to the severity of the emetogenic challenge. If required, additional intravenous doses may be given up to a maximum of 32 mg in 24 hours.

Maximum initial Intravenous doses of 16 mg should be given by slow intravenous infusion over at least 15 minutes, since rapid intravenous administration of ondansetron has been associated with a higher incidence of transient visual disturbances. A single dose greater than 16 mg should not be given (see Section 4.8 Adverse effects (Undesirable effects)).

Dexamethasone sodium phosphate as a single intravenous dose of 20 mg may be given prior to the first intravenous dose of ondansetron before chemotherapy, to potentiate the antiemetic effects of ondansetron.

An alternative to intravenous treatment is a single oral dose of up to 24 mg ondansetron taken with oral dexamethasone 12 mg, 1-2 hours before commencing chemotherapy.

Initial treatment may be followed by oral ondansetron 8 mg 12-hourly or rectal ondansetron 16 mg once daily for up to 5 days to protect against delayed emesis.

Post-operative Nausea and Vomiting (injection only) PONV
For prevention of post-operative nausea and vomiting in adults, ondansetron may be administered as a single dose of 4 mg, given by intramuscular or slow intravenous injection at induction of anaesthesia.

For treatment of established post-operative nausea and vomiting, a single dose of 4 mg given by intramuscular or slow intravenous injection is recommended in most patients. If necessary, the dose may be increased to 8 mg.

PONV Oral Formulations:
For prevention of post-operative nausea and vomiting, the recommended oral dose is 16 mg given 1 hour prior to anaesthesia.
For treatment of established post-operative nausea and vomiting ondansetron administration by injection is recommended

CHILDREN:
Emetogenic chemotherapy and radiotherapy (injection, tablets, oral liquid or wafers)
Experience is currently limited but ondansetron was effective and well tolerated in childrenover the age of 4 years, when given intravenously at a dose of 5 mg/m² over 15 minutes, immediately before chemotherapy, followed by oral therapy at doses of 4 mg twice daily for up
to 5 days. The dose of 5 mg/m² is based on limited data. Suppositories are not recommended for use in children.

Post-operative Nausea and Vomiting (injection only)
For prevention of post-operative nausea and vomiting in children aged 2 to 12 years having surgery under general anaesthesia, ondansetron may be administered by slow intravenous injection (not less than 30 seconds) at a dose of 0.1 mg/kg up to a maximum of 4 mg either prior to, at or after induction of anaesthesia.

For treatment of established post-operative nausea and vomiting, ondansetron may be administered by slow intravenous injection at a dose of 0.1 mg/kg up to a maximum of 4 mg.

PONV in Children and Adolescents aged 1 month to 17 years(injection only)
Slow IV injection (not less than 30 seconds) is recommended for this purpose.

No studies have been conducted on the use of orally administered ondansetron in the prevention or treatment of post-operative nausea and vomiting;

Repeat dosing has not been studied in paediatric patients who experience nausea and/or vomiting despite receiving ondansetron prophylaxis or who continue to experience symptoms after ondansetron treatment.

ELDERLY PATIENTS:
Emetogenic chemotherapy and radiotherapy (injection, tablets, suppositories, wafers or oral liquid)
Efficacy and tolerance in patients aged over 65 years was similar to that seen in younger adults indicating no need to alter dosage or route of administration in the elderly.

CINV and RINV in Elderly Patients
Ondansetron is well tolerated by patients over 65 years of age

Oral Formulation
No alteration of oral dose or frequency of administration is required.

IV Formulation
Elderly patients aged 75 years or older:

- A single dose of intravenous ondansetron given for the prevention of chemotherapy-induced nausea and vomiting (CINV) must not exceed **8mg** (infused over at least 15 minutes).

Adult patients aged less than 75 years:

- A single dose of intravenous ondansetron given for the prevention of CINV in adults (aged less than 75 years) must not exceed **16mg** (infused over at least 15 minutes).

Ondansetron causes a dose-dependent prolongation of the electrocardiographic-corrected QT interval (QTc), which can lead to Torsade de Pointes - a potentially life-threatening heart arrhythmia. Therefore the above new dose restrictions are in place for use of intravenous ondansetron.

Post-operative Nausea and Vomiting (injection only)
There is limited experience in the use of ondansetron in the prevention and treatment of post-operative nausea and vomiting in the elderly.

PATIENTS WITH RENAL IMPAIRMENT: No alteration of daily dosage or frequency of dosing, or route of administration are required.

PATIENTS WITH HEPATIC IMPAIRMENT:
A study which investigated the effect of hepatic impairment on the pharmacokinetics of ondansetron in 24 subjects showed that the plasma clearance of ondansetron is reduced to about 20% of normal, and the serum half-life is significantly prolonged in subjects with severe impairment of hepatic function.

The results in patients with only mildly or moderately impaired hepatic function were less clear. The study showed that in this group the plasma clearance of ondansetron fell to about 50% of that seen in healthy volunteers. Subjects with mild and moderate impairment were not distinguishable from each other for any parameter. This was believed to be partly due to the lack of sensitivity of the Pugh classification system in distinguishing between patients with mild or moderate impairment.

It is recommended that a total daily dose of 8 mg should not be exceeded for patients with moderate or severe hepatic dysfunction. For optimum clinical effect it is recommended that this total daily dose be administered before chemotherapy or radiotherapy.

The severity of the liver disease was assessed according to Pugh's modification of Child's classification (Pugh *et al*, Brit J. Surg. 1973, 60 (8), 646-649). Patients with a Pugh score of 5 or less were considered to have good hepatic function. A patient with a score of 6 was graded as having mild hepatic impairment, 7 to 9 as moderate hepatic impairment and 10 or more as severe hepatic impairment. The clinical features used in the grading and the weighting system applied are shown in the table below:

Clinical and Biochemical Measurements	Points scored for increasing abnormality		
	1	2	3
Encephalopathy (grade) *	None	1 and 2	3 and 4
Ascites	Absent	Slight	Moderate
Bilirubin (µmol per Litre)	17.1-34.2	34.2-51.3	>51.3
Albumin (g per Litre)	35	28-35	<28
Prothrombin time (seconds prolonged)	1-4	4-6	>6
For primary biliary cirrhosis:- Bilirubin (µmol per Litre)	17.1-68.4	68.4-171	>171

* According to grading of Trey, Burns, and Saunders (1966)

Patients with Poor Sparteine/Debrisoquine Metabolism

There were no significant differences among poor and extensive debrisoquine categorised metabolisers with regard to ondansetron disposition (area under the curve, total systemic clearance, elimination half-life) following a single 8 mg intravenous dose. The effect of repeated dosing was not investigated, nevertheless dosage adjustments will probably not be required in patients receiving ondansetron by either the oral or intravenous route.

COMPATIBILITY WITH OTHER DRUGS:

Administration recommendations: slow intravenous injection from an infusion bag or syringe pump. The following drugs may be administered via the Y-site of the ondansetron giving set for ondansetron concentrations of 16 to 160 micrograms/mL (ie. 8 mg/500 mL and 8 mg/50 mL respectively).

Cisplatin: Concentrations up to 0.48 mg/mL (ie. 240 mg in 500 mL) administered over one to eight hours.

Fluorouracil: Concentrations up to 0.8 mg/mL (ie 2.4 g in 3 litres or 400 mg in 500 mL) administered at a rate of at least 20 mL per hour (500 mL per 24 hours). Higher concentrations of fluorouracil may cause precipitation of ondansetron. The fluorouracil infusion may contain up to 0.045% w/v magnesium chloride in addition to other excipients shown to be compatible.

Carboplatin: Concentrations in the range 0.18 mg/mL to 9.9 mg/mL (ie 90 mg in 500 mL to 990 mg in 100 mL), administered over ten minutes to one hour.

Etoposide: Concentrations in the range 0.14 mg/mL to 0.25 mg/mL (ie 72 mg in 500 mL to 250 mg in 1 litre), administered over thirty minutes to one hour.

Ceftazidime: Doses in the range 250 mg to 2000 mg reconstituted with Water for Injections BP as recommended by the manufacturer (ie 2.5 mL for 250 mg and 10 mL for 2 g ceftazidime) and given as an intravenous bolus injection over approximately five minutes.

Cyclophosphamide: Doses in the range 100 mg to 1 g, reconstituted with Water for Injections BP, 5 mL per 100 mg cyclophosphamide, as recommended by the manufacturer, and given as an intravenous bolus injection over approximately five minutes.

Doxorubicin: Doses in the range 10-100 mg reconstituted with Water for Injections BP, 5 mL per 10 mg doxorubicin, as recommended by the manufacturer and given as an intravenous bolus injection over approximately five minutes.

Dexamethasone: Dexamethasone sodium phosphate 20 mg may be administered as a slow intravenous injection over 2-5 minutes. The intravenous administration of dexamethasone should be physically separated from ondansetron either by administration via a different line or by flushing the line with 0.9% Sodium Chloride injection in between the two drugs.

4.3 CONTRAINDICATIONS

Based on reports of profound hypotension and loss of consciousness when ondansetron was administered with apomorphine hydrochloride, concomitant use with apomorphine is contraindicated.

Hypersensitivity to any component of the preparation. (See Section 4.4 Special warnings and precautions for use)

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hypersensitivity reactions have been reported in patients who have exhibited hypersensitivity to other selective 5HT3 receptor antagonists.

Ondansetron prolongs the QT interval in a dose-dependent manner. In addition, post-marketing cases of Torsade de Pointes have been reported in patients using ondansetron. 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 patients with electrolyte abnormalities, congestive heart failure, bradyarrhythmias or patients taking other medicinal products that lead to QT prolongation or electrolyte abnormalities.

Hypokalemia and hypomagnesemia should be corrected prior to ondansetron administration.

Serotonin syndrome has been described following the concomitant use of ondansetron and other serotonergic drugs (see Section 4.5 Interactions with other medicines and other forms of interactions). If concomitant treatment with ondansetron and other serotonergic drugs is clinically warranted, appropriate observation of the patient is advised.

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

Zofran Zydis wafers contain aspartame and therefore should be taken with caution in patients with phenylketonuria.

Repeat dosing has not been studied in paediatric patients who experience nausea and/or vomiting despite receiving ondansetron prophylaxis or who continue to experience symptoms after ondansetron treatment.

Myocardial Ischaemia
Cases of myocardial ischaemia have been reported in patients treated with ondansetron. In some patients, especially in the case of intravenous administration, symptoms appeared immediately after administration of ondansetron. Patients should be alerted to the signs and symptoms of myocardial ischaemia.

Use in the elderly
See Section 4.2 Dose and method of administration.

Paediatric use
See Section 4.2 Dose and method of administration.

Effects on laboratory tests
No data available

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

There is no evidence that ondansetron either induces or inhibits the metabolism of other drugs commonly coadministered with it. Specific studies have shown that there are no pharmacokinetic interactions when ondansetron is administered with alcohol, temazepam, alfentanil, furosemide, tramadol or propofol.

Ondansetron is metabolised by multiple hepatic cytochrome P-450 enzymes: CYP3A4, CYP2D6 and CYP1A2. Due to the multiplicity of metabolic enzymes capable of metabolising ondansetron, enzyme inhibition or reduced activity of one enzyme (e.g. CYP2D6 genetic deficiency) is normally compensated by other enzymes and should result in little or no significant change in overall ondansetron clearance or dose requirement.

Caution should be exercised when ondansetron is coadministered with drugs that prolong the QT interval and/or cause electrolyte abnormalities (see section 4.4 Special warnings and precautions for use).

Based on reports of profound hypotension and loss of consciousness when ondansetron was administered with apomorphine hydrochloride, concominant use with apomorphine is contraindicated.

In patients treated with potent inducers of CYP3A4 (i.e. phenytoin, carbamazepine, and rifampicin), the oral clearance of ondansetron was increased and ondansetron blood concentrations were decreased.

Following a single 8 mg tablet dose of ondansetron, a threefold to fourfold decrease in the systemic exposure has been seen in adult epileptic subjects maintained on chronic doses of carbamazepine (n = 8) or phenytoin (n = 8) and not receiving chemotherapy. The effect of these enzyme inducing agents on intravenous ondansetron has not been assessed, but the absence of any first pass effects would be expected to result in a smaller change in exposure than seen following oral dosing. Due to the limited efficacy data in subjects on antiepileptics and the many variables that may influence exposure and response, the clinical significance of this drug interaction in cancer patients receiving chemotherapy is not known.

Serotonergic Drugs (e.g., SSRIs and SNRIs)
Serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) has been described following the concomitant use of ondansetron and other serotonergic drugs, including selective serotonin reuptake inhibitors (SSRIs) and serotonin noradrenaline reuptake inhibitors (SNRIs) (see Section 4.4. Special warnings and precautions for use).

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility
Oral doses of ondansetron up to 15 mg/kg/day in rats had no effect on male or female fertility.
Women of childbearing potential should consider the use of contraception.

Use in Pregnancy: Pregnancy Category - B1

Based on human experience from epidemiological studies, ondansetron is suspected to cause orofacial malformations when administered during the first trimester of

pregnancy. In one cohort study including 1.8 million pregnancies, first trimester ondansetron use was associated with an increased risk of oral clefts (3 additional cases per 10 000 women treated; adjusted relative risk, 1.24, (95% CI 1.03-1.48)).
The available epidemiological studies on cardiac malformations show conflicting results.
Animal studies does not indicate direct or indirect harmful effects with respect to reproductive toxicity. Ondansetron should not be used during the first trimester of pregnancy.

Use in Lactation:
Tests have shown that ondansetron is excreted in the breast milk of rats. It is therefore recommended that mothers receiving ondansetron should not breast-feed their babies.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1000 and <1/100), rare (≥1/10,000 and <1/1000) and very rare (<1/10,000), including isolated reports. Very common, common and uncommon events were generally determined from clinical trial data. The incidence in placebo was taken into account. Rare and very rare events were generally determined from post-marketing spontaneous data.

The following frequencies are estimated at the standard recommended doses of ondansetron according to indication and formulation. The adverse event profiles in children and adolescents were comparable to that seen in adults

Immune system disorders

Rare:	Immediate hypersensitivity reactions, sometimes severe, including anaphylaxis.

Nervous system disorders

Very common:	Headache.
Uncommon:	Seizures, movement disorders (including extrapyramidal reactions such as oculogyric crisis, dystonic reactions and dyskinesia have been observed without definitive evidence of persistent clinical sequelae).
Rare:	Dizziness during rapid i.v. administration.

Eye disorders

Rare:	Transient visual disturbances (eg blurred vision) predominantly during i.v. administration.
Very rare:	Transient blindness predominantly during i.v. administration.

The majority of the blindness cases reported resolved within 20 minutes. Most patients had received chemotherapeutic agents, which included cisplatin. Some cases of transient blindness were reported as cortical in origin.

Cardiac disorders

Uncommon: Arrhythmias, chest pain with or without ST segment depression, bradycardia.

Rare: QTc prolongation (including Torsade de Pointes)

Unknown: Myocardial ischaemia

Vascular disorders

Common: Sensation of warmth or flushing.

Uncommon: Hypotension.

Respiratory, thoracic and mediastinal disorders

Uncommon: Hiccups.

Gastrointestinal disorders

Common: Constipation.

Xerostomia.

Local anal/rectal burning sensation following insertion of suppositories.

Hepatobiliary disorders

Uncommon: Asymptomatic increases in liver function tests[#].

[#]These events were observed commonly in patients receiving chemotherapy with cisplatin.

Skin and subcutaneous tissue disorders

Very rare: Toxic skin eruption, including toxic epidermal necrolysis.

General disorders and administration site conditions

Common: Local i.v. injection site reactions.

To date there has been limited safety experience in controlled trials following intramuscular administration.

Of 7,400 patients who have received intravenous ondansetron during clinical trials, 11 experienced major cardiovascular events, including 3 fatalities, which were considered to be drug-related by the investigators (1 probable, 10 possible). It is well known that cardiovascular events, especially of a vascular occlusive nature are not uncommon among patients with cancer, and these events are further increased with cytotoxic chemotherapy, particularly cisplatin.

Table 1 shows adverse events occurring in ≥ 1% of paediatric patients (either group) in three pivotal clinical trials for prevention of post-operative nausea and vomiting. Ondansetron appears to be as well tolerated as placebo.

Table 1 - Adverse events occurring in ≥1% of paediatric patients in three pivotal clinical trials for prevention of post-operative nausea and vomiting.

	Placebo (n=548)	Ondansetron (n=542)
Total patients with AE	56% (309)	53% (289)
Eye disorder	16% (86)	19% (102)
Wound problem	13% (72)	13% (70)
Anxiety/agitation	7% (36)	8% (42)
Drowsiness/sedation	8% (44)	6% (34)
Nausea and/or vomiting	11% (62)	6% (33)
Headache	6% (32)	6% (32)
Pyrexia	4% (22)	4% (21)
Disease: lower respiratory tract	1% (6)	3% (16)
Arrhythmia	3% (15)	3% (14)
Expectoration	3% (16)	2% (13)
Cough	2% (13)	2% (13)
Dizziness	2% (11)	2% (11)
Laryngospasm	2% (10)	2% (11)
Disturbance of conduct/behaviour	1% (8)	2% (10)
Hypoxia	1% (6)	1% (8)
Visual disturbance	2% (11)	1% (6)
Bradycardia	<1% (2)	1% (6)
Throat disorder	<1% (2)	1% (6)
Bronchospasm/asthma	2% (10)	<1% (5)
Swollen periocular area	1% (6)	<1% (5)
Gastric symptoms	1% (8)	<1% (4)
Poor oral intake	1% (8)	<1% (4)
Pain	1% (6)	<1% (4)
Haemorrhage	1% (8)	<1% (3)
Ear disorder	1% (6)	<1% (2)

The overall incidence of adverse events was similar for ondansetron (53%) and placebo (56%). The most commonly reported adverse events were eye disorder(s) as a result of ophthalmic operations, wound problems at the surgical site, nausea and/or vomiting, drowsiness/sedation, anxiety/agitation and headache. These events are not unexpected in patients undergoing surgery and there was little difference of these between treatment groups. However the incidence of nausea and/or vomiting reported

as an adverse event was significantly higher in patients who had received placebo (11%) compared to those who had received ondansetron (6%).

Table 2 - Adverse events occurring in ≥1% of paediatric patients in one pivotal clinical trial for treatment of post-operative nausea and vomiting.

	Placebo (n=183)	Ondansetron (n=192)
Nausea and/or vomiting	15% (27)	9% (18)
Wound problem	8% (14)	6% (11)
Pyrexia	10% (19)	5% (10)
Headache	6% (11)	5% (9)
Drowsiness/sedation	7% (12)	4% (7)
Anxiety/agitation	6% (11)	4% (7)
Disturbed behaviour	2% (3)	2% (4)
Hypoxia	<1% (1)	2% (4)
Cough	3% (5)	2% (3)

Fewer adverse events were reported with ondansetron (36%) than with placebo (47%). The most common adverse events were similar to those reported in clinical trials for the prevention of post-operative nausea and vomiting

Occasionally local reactions at the site of intravenous injection have been reported.

Table 3 - Adverse Events occurring in ≥1% of adult patients receiving either ondansetron or placebo IV for the prevention or treatment of post-operative nausea and vomiting

	Placebo (n = 842)	**Ondansetron IV** (n = 1998)
Headache	10% (82)	11% (220)
Dizziness	9% (73)	8% (144)
Constipation	3% (25)	4% (82)
Bradycardia	2% (19)	3% (60)
Drowsiness	2% (18)	3% (59)
Dysuria/Urinary Tract Infection	2% (15)	3% (53)
Injection Site Reaction	2% (21)	2% (47)
Shivering	2% (20)	2% (43)
Nausea/Vomiting	2% (15)	2% (34)
Pruritis	1% (9)	2% (33)
Anxiety	1% (12)	1% (29)
Sleep Disturbance	<1% (5)	1% (29)
Cough	<1% (6)	1% (26)
Urinary retention	1% (10)	1% (24)
Rash	1% (9)	1% (21)
Abdominal Pain	1% (9)	<1% (20)
Hypotension	2% (14)	<1% (19)
Flatulence	1% (9)	<1% (19)

The overall incidence rate was 45% in the placebo group and 47% in the IV ondansetron group.

The neurological body system was associated with the highest incidence of adverse events (placebo approximately 23%; ondansetron 24%). These events were predominantly headache, dizziness and drowsiness.

Cardiovascular adverse events (bradycardia and hypotension) occurred in approximately 4% in both placebo and ondansetron groups; gastrointestinal adverse events (constipation, nausea/vomiting, flatulence and abdominal pain) occurred in approximately 7% of patients both receiving placebo and IV ondansetron.
The incidence rates were generally similar in both treatment groups for all body systems.

Reporting suspected adverse effects
Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Little is at present known about overdosage with ondansetron, however, a limited number of patients received overdoses. Manifestations that have been reported include visual disturbances, severe constipation, hypotension and a vasovagal episode with transient second degree AV block. In all instances, the events resolved completely. There is no specific antidote for ondansetron, therefore in cases of suspected overdose, symptomatic and supportive therapy should be given as appropriate.

Ondansetron prolongs QT interval in a dose-dependent fashion. ECG monitoring is recommended in cases of overdose.

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

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5. PHARMACOLOGICAL PROPERTIES
5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action
Ondansetron is a potent, highly selective $5HT_3$ receptor-antagonist. Its precise mode of action in the control of nausea and vomiting is not known. Chemotherapeutic agents and radiotherapy may cause release of 5HT in the small intestine initiating a vomiting reflex by activating vagal afferents via $5HT_3$ receptors. Ondansetron blocks the initiation of this reflex. Activation of vagal afferents may also cause a release of 5HT in the area postrema, located on the floor of the fourth ventricle, and this may also promote emesis through a central mechanism. Thus, the effect of ondansetron in the management of the nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy is due to antagonism of $5HT_3$ receptors on neurones located both in the peripheral and central nervous system. The mechanisms of action in post-operative nausea and vomiting are not known but there may be common pathways with cytotoxic induced nausea and vomiting. In psychomotor testing ondansetron does not impair performance nor cause sedation. Ondansetron does not alter plasma prolactin concentrations.

A study in cloned human cardiac ion channels has shown ondansetron has the potential to affect cardiac repolarisation via blockade of HERG potassium channels. The clinical relevance of this finding is uncertain.

CLINICAL TRIALS

CHEMOTHERAPY AND RADIOTHERAPY INDUCED NAUSEA AND VOMITING (CINV and RINV)

Adult Studies

Highly emetogenic chemotherapy:
In a double-blind, randomised study 152 patients were given Zofran 8 mg i.v. single dose and 173 patients were given 32 mg iv single dose 30 minutes prior to Cisplatin (≥ 50 mg/m^2). No significant difference in terms of emesis control or grade of nausea was demonstrated between 8 mg or 32 mg. However, in some studies conducted in patients receiving medium (50-90 mg/ m^2) or high doses (≥ 100 mg/ m^2) of cisplatin chemotherapy, the 32 mg single dose has demonstrated a statistically significant superiority over the 8 mg single dose with regard to control of emesis (see section 4.2 Dose and method of administration).

In a double-blind, randomised, cross-over trial, 103 chemotherapy naive patients scheduled to receive cisplatin (50-120 mg/ m^2) chemotherapy were recruited. Ninety-one patients completed both courses of Zofran 0.15 mg/kg (8 mg) i.v. x 3 with or without dexamethasone 20 mg i.v. The combination of Zofran and dexamethasone was shown to be significantly superior to ondansetron alone.

In a randomised, double-blind parallel group study, 420 patients were randomised to receive either Zofran 16 mg suppository prior to cisplatin chemotherapy (≥ 50 mg/m^2) on day 1 followed by Zofran 16 mg suppository once daily for a further 2 days, or Zofran 8 mg i.v. prior to cisplatin chemotherapy followed by Zofran 8 mg orally twice daily for a further 2 days. Results from the primary efficacy analysis (ie ≤ 2 emetic episodes on day 1) show that the Zofran suppository and Zofran i.v. and oral combined regimens are equivalent. However, results from the secondary efficacy analyses (eg number of emetic episodes on Day 1, the worst day of Days 1 - 3 and over all of Days 1 - 3) showed that the Zofran suppository was less effective. Patients on Zofran i.v. and oral combined regimen remained free of emesis for significantly longer than patients receiving Zofran suppository.

In a randomised, double-blind, parallel group study 542 patients were randomised to receive either Zofran tablets (3 x 8mg) plus dexamethasone capsules (2 x 6mg), or i.v. Zofran 8mg plus i.v. dexamethasone 20mg, prior to cisplatin infusion. 24mg of Zofran administered orally was as effective as Zofran 8 mg given i.v. in controlling acute emesis and nausea induced by cisplatin chemotherapy. One Zofran 24mg tablet has been shown to be bioequivalent to three Zofran 8mg tablets.

There are no studies on the use of suppositories in radiation induced nausea and vomiting.

Emetogenic Chemotherapy
In a double-blind, parallel group study 82 patients were randomised to either Zofran 8 mg i.v. prior to cyclophosphamide (≥500 mg/ m^2) based chemotherapy (doxorubicin or epirubicin ≥40 mg/m^2) followed by 8 mg orally three times a day for 3-5 days or metoclopramide 60 mg i.v. prior to chemotherapy followed by 20 mg orally three times a day for 3-5 days. Zofran was shown to be significantly superior to Metoclopramide.

In a randomised, single-blind study, Zofran 8 mg orally twice daily in 155 patients was compared with Zofran 8 mg orally three times daily in 153 patients for 3-5 days following chemotherapy. Zofran 8 mg i.v. was given prior to cyclophosphamide (≥500 mg/m^2) based chemotherapy (doxorubicin or epirubicin >40 mg/m^2) on Day 1. Zofran 8 mg given orally twice daily was as effective as Zofran 8 mg given orally three times daily.

In a randomised, double-blind parallel group study, 406 patients were randomised to receive either Zofran 16 mg suppository once daily for 3 days or Zofran 8 mg orally twice daily for 3 days. The first administration of suppository and tablet began 2 hours and 1-2 hours respectively prior to cyclophosphamide chemotherapy (≥ 500 mg/m^2) on day 1. Results from the primary efficacy analysis (≤ 2 emetic episodes on the worst day of days 1-3) show that the Zofran suppository treatment is equivalent to the Zofran oral treatment. The Zofran suppository was less effective than Zofran oral treatment for a number of other secondary efficacy criteria (complete control of emesis on the worst day of Days 1 - 3, total number of emetic episodes Days 1 - 3 and number of emetic episodes on worst day of Days 1 - 3).

Paediatric Studies
Three open-label, uncontrolled, non-comparative studies have been performed with 182 patients, aged 4-18 years old with cancer who were given a variety of cisplatin or non-cisplatin regimens. In these trials an initial i.v. dose of Zofran was followed by oral administration of Zofran. In these studies, 58% of the 170 evaluable patients had 0 emetic episodes on Day 1.

POST-OPERATIVE NAUSEA AND VOMITING (PONV)

Prevention of PONV

Adult Studies*
Surgical patients received Zofran immediately before the induction of general balanced anaesthesia. In a double-blind, placebo controlled study 136 patients given Zofran 4 mg i.v. immediately prior to general anaesthesia was significantly more effective than placebo.

In a double-blind, placebo controlled study, 207 patients were given a single oral dose of Zofran 16 mg and 204 patients were given placebo one hour prior to induction of anaesthesia. A significantly greater proportion of surgical patients had no emesis during the 0-24 hour post-recovery period compared with placebo.

*The majority of patients included in the prevention of PONV studies using Zofran have been adult women receiving balanced anaesthesia for gynaecological surgery.

Paediatric Studies
Three, large, double-blind, placebo-controlled studies have been performed in 1,049 male and female patients (2 to 12 years of age) undergoing general anaesthesia with nitrous oxide. The surgical procedures included tonsillectomy with or without adenoidectomy, strabismus surgery, herniorrhaphy, and orchidopexy. Patients were randomised to either single i.v. doses of Zofran (0.1 mg/kg for children weighing 40 kg

or less, a single 4 mg dose for children weighing more than 40 kg) or placebo. Study drug was administered over at least 30 seconds, immediately prior to or following anaesthesia induction. Zofran showed significant statistical superiority over placebo in preventing post-operative nausea and vomiting. Repeat dosing was not undertaken in these studies. Children at greater risk of post-operative nausea and vomiting are more likely to benefit from prophylaxis; this includes children with a history of motion sickness or previous post-operative nausea and vomiting. No comparisons with other drugs for the prevention of nausea and/or vomiting are available.

Treatment of PONV

Adults*
Two hundred and twenty one adult surgical patients receiving general balanced anaesthesia, who received no prophylactic anti-emetics and who experienced nausea and/or vomiting within 2 hours post-operatively were evaluated in a double-blind study. Patients who experienced an episode of post-operative nausea and/or vomiting were given Zofran 4 mg i.v. over 2-5 minutes, and this was significantly more effective than placebo.

*The majority of patients treated for PONV in studies using Zofran have been adult women receiving balanced anaesthesia for gynaecological surgery.

Paediatric Study
One, large, double-blind, placebo-controlled study was performed in 351 male and female outpatients (2 to 12 years of age) who received general anaesthesia with nitrous oxide and no prophylactic anti-emetics. Surgical procedures were restricted. Patients who experienced two or more emetic episodes within 2 hours following discontinuation of nitrous oxide were randomised to a single i.v. dose of (0.1 mg/kg for children weighing 40 kg or less, a single 4 mg dose for children weighing more than 40 kg) or placebo administered over at least 30 seconds. Zofran demonstrated statistically significant superiority over placebo in preventing further episodes of nausea and vomiting. Repeat dosing was not a feature of this study. No data, involving comparisons with active treatments, have been evaluated.

5.2 PHARMACOKINETIC PROPERTIES
Absorption, Distribution, Metabolism and Excretion

Following oral dosing with ondansetron, peak plasma concentrations are achieved in approximately 1.5 hours. For doses above 8mg the increase in ondansetron systemic exposure with dose is greater than proportional; this may reflect some reduction in first pass metabolism at higher doses. The absolute bioavailability of the ondansetron tablet is approximately 60% (range 36-112%). The tablet, wafer and oral liquid formulations are bioequivalent.
The terminal elimination half-life of ondansetron after oral dosing is 4.1 to 11.6 hours and after intravenous dosing 2.5 to 6.1 hours.
The half-life may be prolonged in the elderly.

Extent of absorption following intramuscular injection into a lateral compartment of the thigh is identical to intravenous injection and absorption is rapid with T_{max} occurring approximately 10 minutes after administration. The C_{max} after intramuscular administration is 61% lower than that following intravenous administration. In patients

with severe hepatic impairment, systemic clearance is markedly reduced with prolonged elimination half-lives (15-32 h) and an oral bioavailability approaching 100% because of reduced presystemic metabolism. Ondansetron is extensively metabolised in humans, with approximately 5% of a radiolabelled dose recovered as the parent compound from the urine.

The primary metabolic pathway is hydroxylation on the indole ring followed by glucuronide or sulphate conjugation. Although some nonconjugated metabolites have pharmaceutical activity, these are not found in plasma concentrations likely to significantly contribute to the biological activity of ondansetron.

Ondansetron is a substrate for multiple human hepatic cytochrome P-450 enzymes including CYP1A2, CYP2D6 and CYP3A4. This multiplicity of metabolic enzymes capable of metabolising ondansetron means that inhibition or loss of one enzyme (eg. CYP2D6 genetic deficiency) results in little change in overall rates of ondansetron elimination.

The plasma protein binding is 70-76%. The volume of distribution is 1.8 L/kg.

In a study of 21 children aged 3-12 years receiving elective surgery with general anaesthesia, the clearance and volume of distribution of ondansetron following a single intravenous dose of 2 mg (3-7 years old) or 4 mg (8-12 years old) were reduced. The size of the change was age-related with clearance falling from about 300 mL/min at 12 years of age to 100 mL/min at 3 years. Volume of distribution fell from about 75 L at 12 years to 17 L at 3 years.

The clinical safety of ondansetron in children under 2 years has not been established. Increased incidence of mortality with no specific target organ toxicity has been observed in young rats with immature drug metabolising enzymes.

Following rectal administration with an ondansetron suppository, peak plasma concentrations of 15-40 ng/mL are reached in approximately six hours. Plasma concentrations then fall, but at a slower rate than after an oral dose due to continued absorption of ondansetron. The elimination half-life is approximately six hours. Females show a small, clinically insignificant increase in half-life when compared to males. The absolute bioavailability of ondansetron from the suppository is approximately 60%. The relative bioavailability of the suppository compared to an 8 mg tablet was 77%.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity
Ondansetron did not induce mutations in Salmonella typhimurium, Escherichia coli or Chinese Hamster Ovary cells in the presence or absence of metabolic activation, and showed no potential for causing chromosomal damage *in vitro* in peripheral human lymphocytes or *in vivo* in a mouse micronucleus assay. No evidence for DNA damage was observed with ondansetron in a yeast mitotic gene conversion assay.

Carcinogenicity
No evidence for carcinogenic activity was found in two year studies at ondansetron doses up to 10 mg/kg/day by gavage in rats or up to 30 mg/kg/day via drinking water in mice.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Refer to Section 2 - Qualitative and quantitative composition.

6.2 INCOMPATIBILITIES

Ondansetron injection should not be administered in the same syringe or infusion as any other medication.

Ondansetron injection ampoules should not be autoclaved.

Compatibility with intravenous fluids:
Ondansetron injection should only be admixed with those infusion solutions which are recommended.

Ondansetron injection has been shown to be stable for seven days at room temperature (below 25°C) under fluorescent lighting or in a refrigerator with the following intravenous infusion fluids:

Sodium Chloride Intravenous Infusion BP 0.9% w/v

Glucose Intravenous Infusion BP 5% w/v

Mannitol Intravenous Infusion BP 10% w/v

Ringer's Intravenous Infusion

Potassium Chloride 0.3% w/v and Sodium Chloride 0.9% w/v Intravenous Infusion BP

Potassium Chloride 0.3% w/v and Glucose 5% w/v Intravenous Infusion BP

Compatibility studies have been undertaken in polyvinyl chloride infusion bags and polyvinyl chloride administration sets. It is considered that adequate stability would also be conferred by the use of polyethylene infusion bags or type 1 glass bottles. Dilutions of ondansetron in sodium chloride 0.9% w/v or in glucose 5% w/v have been demonstrated to be stable in polypropylene syringes. It is considered that ondansetron injection diluted with other compatible infusion fluids would be stable in polypropylene syringes.

Although the chemical and physical stability of ondansetron injection, diluted with the listed intravenous infusion fluids, has been demonstrated for seven days at room temperature (below 25°C) it is recommended that, in order to reduce microbiological contamination hazards, the diluted solutions should be prepared immediately prior to use and infusion commenced as soon as practicable after preparation of the mixture. The diluted infusion solution should be used within 24 hours and any residue discarded.

Warning: Diluted solutions which are hazy, discoloured or contain visible particulate matter must be discarded

6.3 SHELF-LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30C.

Additional storage conditions:

Oral liquid: Store upright. Do not refrigerate.

Injection: Protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

Zofran tablets 4 mg and 8 mg: PVC/PVDC blister packs of 4, 10, 15, 30 and 90, and bottles of 15, 30, and 100.

Zofran tablets 24 mg: Blister packs of 1 and 5.

Zofran oral liquid: Glass Type III coloured bottles with a PP child resistant closure each containing 50 mL of sugar-free strawberry flavoured oral liquid.

Zofran Zydis wafers: Al/Al blister packs of 4 and 10.

Zofran injections: Clear Type 1 glass syringe with a chlorobutyl plunger (pack of 5) or ampoules (packs of 1, 2, 4, 5 and 10).

Zofran suppositories: Blister pack of 5.

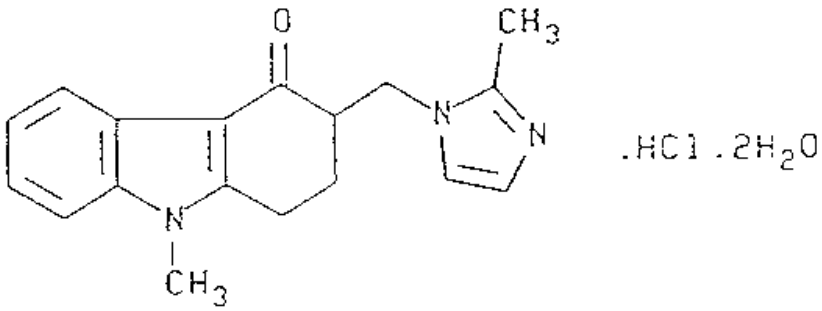
Not all strengths, dose forms, pack sizes and container types are being distributed in Australia.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia , any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



ondansetron hydrochloride dihydrate

CAS NUMBER: 99614-01-4 (ondansetron hydrochloride dihydrate)
99614-02-5 (ondansetron)

Description

The chemical name of ondansetron hydrochloride dihydrate is 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one,hydrochloride dihydrate. The molecular formula of ondansetron hydrochloride dihydrate is $C_{18}H_{19}N_30.HCl.2H_20$ and the relative molecular mass is 365.9. It takes the form of a white to off-white powder with a melting point of 177°C. It is sparingly soluble in water and in alcohol, soluble in methanol and slightly soluble in methylene chloride. It is soluble in saline (0.9% w/v) to about 8mg/mL. The pKa of ondansetron hydrochloride dihydrate as determined by a solubility procedure is 7.4. The distribution coefficient between n-octanol and water is pH dependent with log D = 2.2 at a pH of 10.6 and log D = 0.6 at a pH of 5.95.

The chemical name of ondansetron is 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one. The molecular formula of ondansetron is $C_{18}H_{19}N_30$ and the relative molecular mass is 293.4. It takes the form of a white to off-white powder with a melting point of approximately 230°C. Ondansetron is 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. Ondansetron is soluble in chloroform and slightly soluble in acetonitrile and methanol. The pKa of ondansetron as determined by UV monitored partition method is 7.8. The partition coefficient, log P in n-octanol : water is 2.14.

7.MEDICINE SCHEDULE (POISONS STANDARD)

S4

8.SPONSOR

Aspen Pharmacare Australia Pty Ltd
34-36 Chandos Street
St Leonards NSW 2065
Australia.
http://www.aspenpharma.com.au

9. DATE OF FIRST APPROVAL

17 April 1991

10. DATE OF REVISION

26 May 2022

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.9	Cases consistent with serotonin syndrome have been reported in young children following oral overdose.
4.2	Clarification of doses in children

4.6	Update on use in pregnancy
1,2 & 3	Injections, 24mg tablet and suppositories are no longer marketed
2,3	Update to strawberry flavour for Zofran Zydis
All	Minor editorial changes
6.5	Update packaging material to align with ARTG
2	Strawberry flavour changed to SC887891 (ARTG PI No: 140281).
2	Minor editorial changes
2	Sorbitol quantified
4.4 & 4.8	Myocardial ischaemia