

AUSTRALIAN PRODUCT INFORMATION ONDANSETRON KABI (ONDANSETRON HYDROCHLORIDE DIHYDRATE)

1 NAME OF THE MEDICINE

Ondansetron hydrochloride dihydrate.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION / 3 PHARMACEUTICAL FORM

Ondansetron 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 8 mg/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.

Each ampoule of Ondansetron Kabi contains 2 mg/mL ondansetron (as hydrochloride dihydrate) as the active ingredient and the following excipients: sodium chloride, citric acid monohydrate, sodium citrate dihydrate, water for injections.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Ondansetron 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 dose of ondansetron should be flexible in the range of 8 to 32 mg a day and selected as shown below. The lowest effective dose should be used.

ADULTS

Emetogenic Chemotherapy and Radiotherapy

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.

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.

Maximal 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 **4.4 Special warnings and precautions for use**).

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.

Post-Operative Nausea and Vomiting 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.

CHILDREN

Emetogenic Chemotherapy and Radiotherapy

Experience is currently limited but ondansetron was effective and well tolerated in children over 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.

Post-Operative Nausea and Vomiting

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

Slow IV Injection (not less than 30 seconds) is recommended for this purpose.

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.

USE IN THE ELDERLY

Emetogenic Chemotherapy and Radiotherapy

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.

Chemotherapy- and Radiotherapy- Induced Nausea and Vomiting

Ondansetron is well tolerated by patients over 65 years of age.

Elderly Patients

Elderly patients aged 75 years or older:

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

Adult patients aged less than 75 years:

A single dose of intravenous ondansetron given for prevention of chemotherapy induced nausea and vomiting must not exceed **16 mg** (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 dose restrictions are in place for use of intravenous ondansetron.

Post-Operative Nausea and Vomiting

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 intravenous route.

Compatibility and Stability with Intravenous Fluids and Other Medicines

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 $\mu\text{g}/\text{mL}$ (*i.e.* 8 mg/500 mL and 8 mg/50 mL respectively).

- **Cisplatin**: Concentrations up to 0.48 mg/mL (*i.e.* 240 mg in 500 mL) administered over one to eight hours.
- **Fluorouracil**: Concentrations up to 0.8 mg/mL (*i.e.* 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 (*i.e.* 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 (*i.e.* 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 (*i.e.* 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 1000 mg, 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 to 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 two to five 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.

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 (see also **Pharmaceutical Precautions**):

- 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.

Pharmaceutical Precautions

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. If storage is necessary, hold at room temperature (below 25°C) for not more than 6 hours and any residue discarded.

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

Ondansetron injection is for single use in one patient only. Discard any residue.

Ondansetron injection and diluted solutions should be protected from light.

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

Ondansetron injection ampoules should not be autoclaved.

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 5-HT₃ 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 **4.5 Interactions with other medicines and other forms of interactions**). If concomitant treatment with ondansetron and other serotonergic medicines 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.

Use in the elderly

No data available.

Paediatric Use

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.

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 medicines commonly co-administered 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 co-administered with drugs that prolong the QT interval and/or cause electrolyte abnormalities (see **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, concomitant 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 anti-epileptics and the many variables that may influence exposure and response, the clinical significance of any potential interaction between intravenous ondansetron and CYP3A4 inducers in chemotherapy patients 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 do 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 ($\geq 1/10$), common ($\geq 1/100$ and $< 1/10$), uncommon ($\geq 1/1000$ and $< 1/100$), rare ($\geq 1/10,000$ 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 IV administration.

Eye Disorders

Rare: Transient visual disturbances (eg. blurred vision) predominantly during IV administration.

Very rare: Transient blindness predominantly during IV 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).

Vascular Disorders

Common: Sensation of warmth or flushing.

Uncommon: Hypotension.

Respiratory, Thoracic and Mediastinal Disorders

Uncommon: Hiccups.

Gastrointestinal Disorders

Common: Constipation, xerostomia.

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 IV 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 $\geq 1\%$ 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 $\geq 1\%$ 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)

	Placebo (n = 548)		Ondansetron (n = 542)	
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 $\geq 1\%$ 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 $\geq 1\%$ of adult patients receiving either ondansetron or placebo IV for the prevention or treatment of post-operative nausea and vomiting

	Placebo (n = 842)		Ondansetron (n = 1,998)	
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 of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions at <http://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.

For information on the management of overdose, contact the Poison Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of Action

Ondansetron is a potent, highly selective 5-HT₃ 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 5-HT in the small intestine initiating a vomiting reflex by activating vagal afferents via 5-HT₃ receptors. Ondansetron blocks the initiation of this reflex. Activation of vagal afferents may also cause a release of 5-HT 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 5-HT₃ 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

Adult Studies

Highly Emetogenic Chemotherapy

In a double-blind, randomised study, 152 patients were given ondansetron 8 mg IV single dose and 173 patients were given 32 mg IV single dose 30 minutes prior to cisplatin (≥ 50 mg/m²). 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/m²) or high doses (≥ 100 mg/m²) 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 **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/m²) chemotherapy were recruited. Ninety-

one patients completed both courses of ondansetron 0.15 mg/kg (8 mg) IV × 3 with or without dexamethasone 20 mg IV. The combination of ondansetron and dexamethasone was shown to be significantly superior to ondansetron alone.

Emetogenic Chemotherapy

In a double-blind, parallel group study, 82 patients were randomised to either ondansetron 8 mg IV prior to cyclophosphamide (≥ 500 mg/m²) based chemotherapy (doxorubicin or epirubicin ≥ 40 mg/m²) followed by 8 mg orally three times a day for 3–5 days or metoclopramide 60 mg IV prior to chemotherapy followed by 20 mg orally three times a day for 3–5 days. Ondansetron was shown to be significantly superior to metoclopramide.

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 IV dose of ondansetron was followed by oral administration of ondansetron. 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 Study*

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

* The majority of patients included in the prevention of PONV studies using ondansetron 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 (2–12 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 IV doses of ondansetron (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 medication was administered over at least 30 seconds, immediately prior to or following anaesthesia induction. Ondansetron showed significant statistical superiority over placebo in preventing PONV. Repeat dosing was not undertaken in these studies. Children at greater risk of PONV are more likely to benefit from prophylaxis; this includes children with a history of motion sickness or previous PONV. No comparisons with other medicines for the prevention of nausea and/or vomiting are available.

Treatment of PONV

Adult Study*

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 ondansetron 4 mg IV over 2–5 minutes, and this was significantly more effective than placebo.

* The majority of patients treated for PONV in studies using ondansetron 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 (2–12 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 IV 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. Ondansetron 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

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.

Distribution

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

Metabolism

Ondansetron is extensively metabolised in humans, with approximately 5% of a radio-labelled 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 non-conjugated 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 (e.g. CYP2D6 genetic deficiency) results in little change in overall rates of ondansetron elimination.

Excretion

The terminal elimination half-life of ondansetron after intravenous dosing is 2.5–6.1 hours. The half-life may be prolonged in the elderly. In patients with severe hepatic impairment, systemic clearance is markedly reduced with prolonged elimination half-lives (15–32 hours) because of reduced pre-systemic metabolism.

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.

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. PHARMACOLOGICAL PARTICULARS

6.1 List of excipients

Refer to Section 2 - Qualitative and quantitative composition.

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

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

Stored below 30°C. Protect from light.

6.5 Nature and contents of container

Ondansetron Kabi is intended for intravenous or intramuscular administration.

It is a clear, colourless solution free of visible particles and is packed in an ampoule (clear Type I glass) containing 2 mg/mL ondansetron (as hydrochloride dihydrate) as the active ingredient.

Ondansetron Kabi is available in the following presentations:

- 4 mg/2 mL AUST R 191018 (pack size: 1s, 5s & 10s)
- 8 mg/4 mL AUST R 188775 (pack size: 1s, 5s & 10s)

* Not all pack sizes may be marketed

6.6 Special precautions for disposal

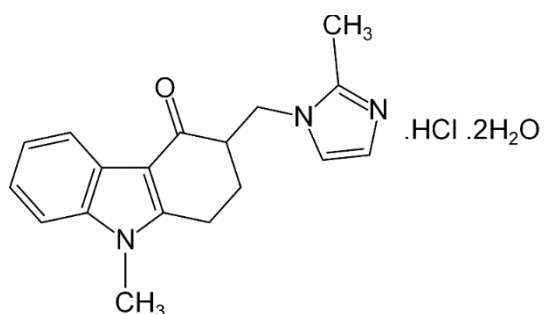
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 Physicochemical properties

Chemical Structure

Ondansetron chemical name is 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one, hydrochloride dihydrate.

Ondansetron hydrochloride dihydrate has the following chemical structure:



Molecular formula: C₁₈H₁₉N₃O.HCl.2H₂O

Molecular weight: 365.9

CAS number:

99614-01-4

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4 - Prescription Only Medicine

8. SPONSOR

Fresenius Kabi Australia Pty Limited

Level 2, 2 Woodland Way

Mount Kuring-gai NSW 2080

Australia

Telephone: (02) 9391 5555

9. DATE OF FIRST APPROVAL

28 November 2012

10. DATE OF REVISION

28th May 2020

SUMMARY TABLE OF CHANGES

Summary table of changes

Section Changed	Summary of new information
all	New format
4,2	Clarification of doses in children
4.6	Update on use in pregnancy

