AUSTRALIAN PRODUCT INFORMATION – ONDANSETRON ODT VTRS (ONDANSETRON) ORALLY DISINTEGRATING TABLETS

1 NAME OF THE MEDICINE

Ondansetron

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ONDANSETRON ODT VTRS is available as orally disintegrating tablets containing 4 mg & 8 mg ondansetron.

Excipient of known effect: lactose monohydrate and aspartame.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

ONDANSETRON ODT VTRS 4
White to off-white, round tablets debossed with '5' on one side and 'E' on the other side with an embossed circular edge.

ONDANSETRON ODT VTRS 8
White to off-white, round tablets debossed with '7' on one side and 'E' on the other side with an embossed circular edge.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Ondansetron is indicated for the prevention and treatment of nausea and vomiting induced by cytotoxic therapy and radiotherapy.

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

The ONDANSETRON ODT VTRS tablet is administered by placing on top of the tongue where it will rapidly disperse, then should be swallowed.

(Note: ONDANSETRON ODT VTRS may take about 60 seconds to disintegrate on the tongue. This may be longer than time required for other similar orally disintegrating products containing ondansetron. We have however demonstrated that the rate and extent of absorption is not compromised due to longer disintegration time of our product.)

ADULTS

Emetogenic chemotherapy and radiotherapy
For the control of chemotherapy or radiotherapy induced emesis or nausea in adults, two oral doses of 8 mg each at 12 hourly intervals may be given (tablets or orally disintegrating tablets), the first dose being administered 2 hours prior to chemotherapy or radiotherapy. To protect against delayed emesis after the first 24 hours, ondansetron should be continued orally at a dosage of 8 mg twice daily for up to 5 days after a course of treatment.

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.

PONV in Children and Adolescents (aged 1 month to 17 years)
Oral Formulations
No studies have been conducted on the use of orally administered ondansetron in the prevention or treatment of post-operative nausea and vomiting.

ELDERLY PATIENTS

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.

CINV and RINV in Elderly Patients
Ondansetron is well tolerated by patients over 65 years of age.
Oral Formulations
No alteration of oral dose or frequency of administration is required.

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:

Table 1: Grading of hepatic impairment

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.

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 $5HT_3$ 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.

ONDANSETRON ODT VTRS tablets 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.

Each 4 mg orally disintegrating tablet contains 10 mg of lactose and each 8 mg orally disintegrating tablet contains 20 mg of lactose. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption who are on a lactose free diet should take this amount into consideration.

Myocardial Ischaemia

Cases of myocardial ischaemia have been reported in patients treated with ondansetron. In some patients, especially in 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

No data available

Paediatric use

No data available

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 interaction when ondansetron is administered alcohol, temazepam, alfentanil, 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 4.5 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 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 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% CL 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.

Category B1: defined as "Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have not shown evidence of an increased occurrence of foetal damage.

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 (e.g. 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.

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 2 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 2: 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 3: 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 4: 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 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Ondansetron is a potent, highly selective 5HT3 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 5HT3 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 5HT3 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 i.v. single dose and 173 patients were given 32 mg i.v. 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 ondansetron 0.15 mg/kg (8 mg) i.v. x 3 with or without dexamethasone 20 mg i.v. The combination of ondansetron 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 ondansetron 16 mg suppository prior to cisplatin chemotherapy (≥ 50 mg/m^2) on day 1 followed by ondansetron 16 mg suppository once daily for a further 2 days, or ondansetron 8 mg i.v. prior to cisplatin chemotherapy followed by ondansetron 8 mg orally twice daily for a further 2 days. Results from the primary efficacy analysis (i.e. ≤ 2 emetic episodes on day 1) show that the ondansetron suppository and ondansetron i.v. and oral combined regimens are equivalent. However, results from the secondary efficacy analyses (e.g. number of emetic episodes on Day 1, the worst day of Days 1 - 3 and over all of Days 1 - 3) showed that the ondansetron suppository was less effective. Patients on ondansetron i.v. and oral combined regimen remained free of emesis for significantly longer than patients receiving ondansetron suppository.

In a randomised, double-blind, parallel group study 542 patients were randomised to receive either ondansetron tablets (3 x 8mg) plus dexamethasone capsules (2 x 6mg), or i.v. ondansetron 8 mg plus

i.v. dexamethasone 20 mg, prior to cisplatin infusion. Administered orally, 24 mg of ondansetron was as effective as ondansetron 8 mg given i.v. in controlling acute emesis and nausea induced by cisplatin chemotherapy. One ondansetron 24 mg tablet has been shown to be bioequivalent to three ondansetron 8 mg 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 ondansetron 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. Ondansetron was shown to be significantly superior to Metoclopramide.

In a randomised, single-blind study, ondansetron 8 mg orally twice daily in 155 patients was compared with ondansetron 8 mg orally three times daily in 153 patients for 3-5 days following chemotherapy. Ondansetron 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. Ondansetron 8 mg given orally twice daily was as effective as ondansetron 8 mg given orally three times daily.

In a randomised, double-blind parallel group study, 406 patients were randomised to receive either ondansetron 16 mg suppository once daily for 3 days or ondansetron 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/m2) on day 1. Results from the primary efficacy analysis (≤ 2 emetic episodes on the worst day of days 1-3) show that the ondansetron suppository treatment is equivalent to the ondansetron oral treatment. The ondansetron suppository was less effective than ondansetron 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 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)

<u>Prevention of PONV</u>

Adult Studies*
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 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 ondansetron 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 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 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 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 drug was administered over at least 30 seconds, immediately prior to or following anaesthesia induction. Ondansetron 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

Adult Studies*

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 i.v. 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 Studies

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. 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

Following oral dosing with ondansetron, peak plasma concentrations are achieved in approximately 1.5 hours. For doses above 8 mg 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%).

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 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 (e.g. CYP2D6 genetic deficiency) results in little change in overall rates of ondansetron elimination.

Excretion

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. 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.

Children

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 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

ONDANSETRON ODT VTRS tablets contain the following inactive ingredients: Mannitol, crospovidone, microcrystalline cellulose, aspartame, colloidal anhydrous silica, magnesium stearate and strawberry guarana.

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

Store below 25°C. Protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

ONDANSETRON ODT VTRS 4 & 8 orally disintegrating tablets (4 & 8 mg ondansetron) are presented in pack sizes* of 4, 10 or 20 tablets in PVC/OPA/Alu/PVC-Peelable lidding foil blister strips.

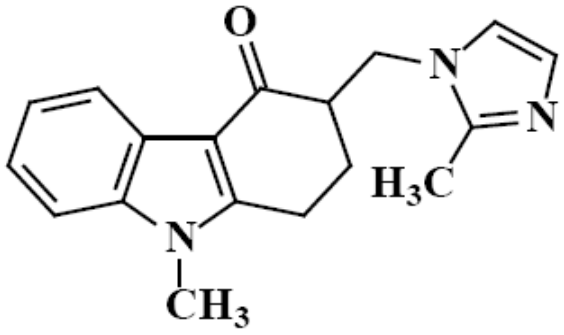
*Some of these pack sizes are not marketed.

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



Active ingredient:	Ondansetron
Chemical name:	3RS-1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one
Molecular weight:	293.4
Molecular formula:	$C_{18}H_{19}N_3O$

It is a white to off-white powder. Ondansetron is very soluble in acid solution, practically insoluble in water.

CAS number

99614-02-5

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 (Prescription Only Medicine)

8 SPONSOR

Helix Pharmaceuticals Pty Ltd
C/-EGA Corporate Advisers Pty Ltd
Level 12, 468 St Kilda Rd
Melbourne VIC 3004

Contact: info@helixpharmaceuticals.com.au

9 DATE OF FIRST APPROVAL

22 January 2024

10 DATE OF REVISION

25 September 2025

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
8	Sponsor details updated
ALL	Change trade name