1 PRODUCT NAME

Ondansetron-Baxter 2mg/mL solution for injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient

Ondansetron-Baxter, solution for injection contains 2.49mg ondansetron hydrochloride dihydrate, equivalent to 2mg ondansetron, per mL.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.

Ondansetron-Baxter is a colourless solution.

The pH of the solution is 3.30 – 4.00.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Ondansetron-Baxter is indicated for:

- the prevention and treatment of nausea and vomiting induced by cytotoxic therapy and radiotherapy,
- the prevention and treatment of post-operative nausea and vomiting.

4.2 Dose and method of administration

For Intramuscular (IM) or Intravenous (IV) use.

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

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 stored under refrigeration (2 - 8°C) and used within 24 hours. The product is for single use in one patient only. Any residue should be discarded.

Adults

Emetogenic chemotherapy and radiotherapy

For the control of chemotherapy or radiotherapy induced emesis or nausea in adults, a single dose of 8mg of ondansetron should be administered as a slow intravenous (IV) injection in not less than 30 seconds, or intramuscular injection (IM), immediately before treatment.

Oral treatment is recommended to protect against delayed or prolonged emesis after the first 24 hours.

Highly emetogenic chemotherapy

For patients receiving highly emetogenic chemotherapy, e.g. high-dose cisplatin, ondansetron may be administered as a single 8mg intravenous or intramuscular dose by slow intravenous injection in not less than 30 seconds, or intramuscular injection, immediately before chemotherapy.

- A single dose of greater than 8mg and up to a maximum of 16mg of ondansetron may only be given by intravenous infusion diluted in 50 - 100mL of saline or other compatible infusion fluid and infused over not less than 15 minutes.
- A single dose of greater than 16mg should not be given due to dose dependent increase of QT prolongation risk (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Alternatively, a dose of 8mg of ondansetron may be administered by slow intravenous injection in not less than 30 seconds or intramuscular injection immediately before chemotherapy, followed by two further intravenous or intramuscular doses of 8mg given no less than four hours apart, or by a constant infusion of 1mg/hour for up to 24 hours.

The selection of dose regimen should be determined by the severity of the emetogenic challenge.

The efficacy of ondansetron in highly emetogenic chemotherapy may be enhanced by the addition of a single intravenous dose of dexamethasone sodium phosphate, 20mg administered prior to chemotherapy.

Oral treatment is recommended to protect against delayed or prolonged emesis after the first 24 hours.

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

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

Children and adolescents:
Emetogenic chemotherapy and radiotherapy (Age 6 months to 17 years)
In children with a body surface area of 0.6 - 1.2m^2 **Ondansetron-Baxter** may be administered as a single IV dose of 5mg/m^2 immediately before chemotherapy, followed by an oral dose of 4mg twelve hours later. It may be necessary to provide ongoing medication using an appropriate oral dose form (4mg twice daily) for up to 5 days after a course of treatment.

For children with a body surface area > 1.2m^2 an initial IV dose of 8mg is administered immediately before chemotherapy, followed by an oral dose of 8mg twelve hours later. It may be necessary to provide ongoing medication using an appropriate oral dose form (8mg twice daily) for up to 5 days after a course of treatment.

Alternatively, in children aged 6 months or more, **Ondansetron-Baxter** may be administered as a single IV dose of 0.15mg/kg (maximum dose 8mg) immediately prior to chemotherapy. This dose may be repeated every 4 hours for a total of 3 doses. It may be necessary to provide ongoing medication using an appropriate oral dose form (4mg twice daily) for up to 5 days after a course of treatment. Adult doses must not be exceeded.

Post-operative nausea and vomiting (Age 1 month to 17 years)
For prevention of post-operative nausea and vomiting in children having surgery under general anaesthesia, ondansetron may be administered by slow IV injection at a dose of 0.1mg/kg up to a maximum of 4mg either prior to, at or after induction of anaesthesia.

Elderly patients

Emetogenic chemotherapy and radiotherapy

In patients 65 to 74 years of age, the dose schedule for adults can be followed. All iv doses should be diluted in 50-100mL of saline or other compatible infusion fluid and infused over 15 minutes.

In patients 75 years of age or older, the initial intravenous dose of ondansetron should not exceed 8mg. All intravenous doses should be diluted in 50-100mL of saline or other compatible infusion fluid and infused over 15 minutes. The initial dose of 8mg may be followed by two further intravenous doses of 8mg, infused over 15 minutes and given no less than four hours apart (see section 5.2).

The above dose restrictions are in place due to the risk of dose-dependent QT prolongation, which can lead to Torsade de Pointes (see section 5.2).

Post-operative nausea and vomiting

There is limited experience in the use of ondansetron in the prevention and treatment of postoperative nausea and vomiting in the elderly.

Impaired renal function

No alteration of daily dosage or frequency of dosing, or route of administration are required.

Impaired hepatic function

Clearance of ondansetron is significantly reduced and the serum half-life significantly prolonged in subjects with moderate or severe impairment of hepatic function. It is recommended that a total daily dose of 8mg should not be exceeded for patients with moderate or severe hepatic dysfunction.

Patients with poor sparteine/debrisoquine metabolism

There is no significant differences in the elimination half-life of ondansetron in patients classified as poor metabolisers of sparteine and debrisoquine. Repeat dosing will result in exposure levels similar to those of the general population. Dosage adjustments are not required.

Compatibility with other medicines

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

Cisplatin

Concentrations up to 0.48mg/mL (i.e. 240mg in 500mL) administered over 1 - 8 hours.

Fluorouracil (5FU)

Concentrations up to 0.8mg/mL (i.e. 2.4g in 3 litres or 400mg in 500mL) administered at a rate of at least 20mL per hour (500mL 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 0.18mg/mL to 9.9mg/mL (i.e. 90mg in 500mL to 990mg in 100mL), administered over ten minutes to one hour.

Etoposide

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

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

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

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

4.3 Contraindications
Hypersensitivity to any component of the preparation (see section 4.4).

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

4.4 Special warnings and precautions for use
Ondansetron hydrochloride solution for injection should not be administered in the same syringe or infusion as any other medication.

Ondansetron-Baxter should only be admixed with the infusion solutions recommended below. It is stable for 36 hours in these infusion solutions when kept under refrigeration (2 - 8°C).

Sodium chloride IV Infusion BP 0.9% w/v
Glucose IV Infusion BP 5% w/v
Mannitol IV Infusion BP 10% w/v
Ringer's IV Infusion
Potassium chloride 0.3% w/v and Sodium chloride 0.9% w/v IV Infusion BP
Potassium chloride 0.3% w/v and Glucose 5% w/v IV 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.

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 stored under refrigeration (2-8 ºC) and used within 24 hours. Any residue should be discarded.

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

The product is for single use in one patient only. Any residue should be discarded.

Identified precautions
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). 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.

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 hepatic impairment
See section 4.2.

Use in renal impairment
See section 4.2.

Use in the elderly
See section 4.2.

Paediatric use
See section 4.2.

Effects on laboratory tests
No data available.

4.5 Interaction with other medicines and other forms of interaction

There is no evidence that ondansetron either induces or inhibits the metabolism of other drugs 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 section 4.4).

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 e.g. phenytoin, carbamazepine, and rifampicin, the oral clearance of ondansetron was increased and ondansetron blood concentrations were decreased.

Following a single 8mg 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).Data from small studies indicate that ondansetron may reduce the analgesic effect of tramadol.

4.6 Fertility, pregnancy and lactation

Fertility
Oral doses of ondansetron up to 15mg/kg/day in rats had no effect on male or female fertility.

Women of childbearing potential should consider the use of contraception.

Pregnancy
Australian categorisation 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 is not recommended during the first trimester of pregnancy.

Breast-feeding
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 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 IV administration.

Eye disorders
Rare: Transient visual disturbances (e.g. 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*).
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. However, 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 > 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	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 of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continuing monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/

4.9 Overdose
Little is at present known about overdosage with ondansetron, however, a limited number of patients have 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 the 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 advice on the management of overdose please contact the National Poisons Centre on phone number: 0800 764 766 [0800 POISON] in New Zealand (or 131126 in Australia).

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group
Antiemetics and Antinauseants, A04AA Serotonin (5HT3) antagonists.

ATC code
A04AA.

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.

QT prolongation
The effect of ondansetron on the QTc interval was evaluated in a double blind, randomised, placebo and positive (moxifloxacin) controlled, crossover study in 58 healthy adult men and women.

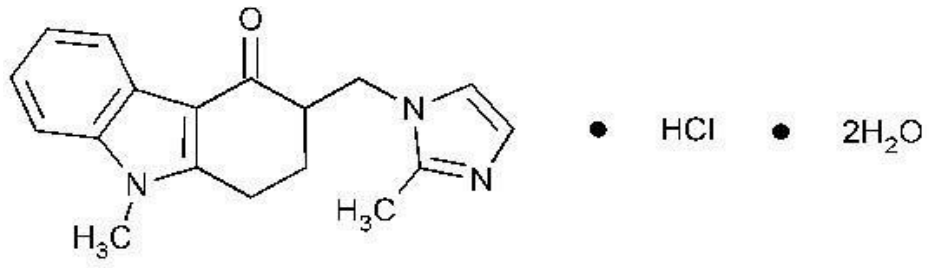
Ondansetron doses included 8mg and 32mg infused intravenously over 15 minutes. At the highest tested dose of 32mg, the maximum mean (upper limit of 90 % CI) difference in QTcF from placebo after baseline-correction was 19.6 (21.5) milliseconds. At the lower tested dose of 8mg, the maximum mean (upper limit of 90 % CI) difference in QTcF from placebo after baseline-correction was 5.8 (7.8) milliseconds.

In this study, there were no QTcF measurements greater than 480 milliseconds and no QTcF prolongation was greater than 60 milliseconds.

Physicochemical properties
Ondansetron hydrochloride dihydrate is a white to off-white powder which is sparingly soluble in water and alcohol.

Ondansetron-Baxter, Solution for Injection, is a clear colourless solution. The pH of the solution is 3.30 – 4.00.

Chemical structure



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

Chemical formula
$C_{18}H_{19}N_3O.HCl.2H_2O$

Molecular weight
365.9

CAS number
99614-01-4

5.2 Pharmacokinetic properties

The disposition of ondansetron following oral, IM or IV dosing is similar with a terminal elimination half-life of about 3 hours and steady state volume of distribution of about 140L.

Equivalent systemic exposure is achieved after intramuscular and intravenous administration of ondansetron. Ondansetron is not highly protein bound (70 - 76%).

Ondansetron is cleared from the systemic circulation predominantly by hepatic metabolism through multiple enzymatic pathways. Less than 5% of the absorbed dose is excreted unchanged in the urine. The absence of the enzyme CYP2D6 (the debrisoquine polymorphism) has no effect on ondansetron's pharmacokinetics. The pharmacokinetic properties of ondansetron are unchanged on repeat dosing. Studies in healthy elderly volunteers have shown slight, but clinically insignificant, age-related increases in both oral bioavailability and half-life of ondansetron.

Gender differences were shown in the disposition of ondansetron, with females having a greater rate and extent of absorption following an oral dose and reduced systemic clearance and volume of distribution (adjusted for weight).

In a clinical study, 51 paediatric patients aged 1 to 24 months received either 0.1 or 0.2mg/kg ondansetron prior to undergoing surgery. Patients aged 1 to 4 months had a clearance when normalised to body weight that was approximately 30% slower than in patients aged 5 to 24 months but comparable to the patients aged 3 to 12 years. The half-life in the 1 to 4 month patient population was reported to average 6.7 hours compared to 2.9 hours for patients in the 5 to 24 month and 3 to 12 year age range. No dose adjustment is necessary for patients aged 1 to 4 months as only a single IV dose of ondansetron is recommended for the treatment of postoperative nausea and vomiting. The differences in pharmacokinetic parameters can be explained in part by the higher volume of distribution in the 1 to 4 month patient population.

In a study of 21 paediatric patients aged between 3 and 12 years undergoing elective surgery with general anaesthesia, the absolute values for both the clearance and volume of distribution of ondansetron following a single intravenous dose of 2mg (3 - 7 years old) or 4mg (8 - 12 years old) were reduced in comparison to values with adult patients. Both parameters increased in a linear fashion with weight and by 12 years of age, the values were approaching those of young adults. When clearance and volume of distribution values were normalised by body weight, the values for these parameters were similar between the different age group populations. Use of weight-based dosing (0.1mg/kg up to 4mg maximum) compensates for these changes and is effective in normalising systemic exposure in paediatric patients.

Population pharmacokinetic analysis was performed on 74 patients aged 6 to 48 months following administration of 0.15mg/kg IV ondansetron every 4 hours for three doses for the treatment of chemotherapy induced nausea and vomiting and 41 surgery patients aged 1 to 24 months following administration of a single 0.1mg/kg or 0.2mg/kg IV dose of ondansetron. Based on the population pharmacokinetic parameters for subjects aged 1 month to 48 months, administration of a 0.15mg/kg IV dose of ondansetron every 4 hours for 3 doses would result in a systemic exposure (AUC) comparable to that observed in paediatric surgery subjects aged 5 to 24 months and previous paediatric studies in cancer (aged 4 to 18 years) and surgical (aged 3 to 12 years) subjects, at similar doses.

In patients with moderate renal impairment (creatinine clearance 15 - 60mL/min), both systemic clearance and volume of distribution are reduced, resulting in a slight, but clinically insignificant,

increase in elimination half-life (5.4h). A study in patients with severe renal impairment who required regular haemodialysis (studied between dialyses) showed ondansetron's pharmacokinetics to be essentially unchanged. In patients with severe hepatic impairment, ondansetron's systemic clearance is markedly reduced with prolonged elimination half-lives (15 - 32h) and an oral bioavailability approaching 100% due to reduced pre-systemic metabolism

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 DMA 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 10mg/kg/day by gavage in rats or up to 30mg/kg/day via drinking water in mice.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid monohydrate
Sodium citrate
Sodium chloride and
Water for injections.

6.2 Incompatibilities

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

Ondansetron-Baxter should only be admixed with those infusion solutions which are recommended.

See also sections 4.4 and 4.2.

6.3 Shelf life

36 months from date of manufacture. The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store at or below 30°C.

6.5 Nature and contents of container

Packs contain either 1 or 5 ampoules.

Each ampoule of **Ondansetron-Baxter** Injection 4mg/2mL contains ondansetron hydrochloride equivalent to ondansetron 4mg.

Each ampoule of **Ondansetron-Baxter** Injection 8mg/4mL contains ondansetron hydrochloride equivalent to ondansetron 8mg.

Not all pack sizes may be available.

6.6 Special precautions for disposal and other handling

Any unused medicine or waste material should be disposed of by taking to your local pharmacy.

7 MEDICINE SCHEDULE

Prescription only medicine.

8 SPONSOR

Ondansetron-Baxter is distributed in New Zealand by:

Baxter Healthcare Ltd
33 Vestey Drive
Mt Wellington
Auckland 1060.

Baxter Healthcare Ltd
PO Box 14 062
Panmure
Auckland 1741

Phone (09) 574 2400.

Ondansetron-Baxter is distributed in Australia by:
Baxter Healthcare Pty Ltd [ABN: 43 000 392 781]
1 Baxter Drive
Old Toongabbie, NSW 2146.

9 DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine:
3 September 2009.

10 DATE OF REVISION OF THE TEXT

31 October 2024

SUMMARY TABLE OF CHANGES

Section	Summary of new information
All	Consistent headings, editorial changes for readability, formatting and spelling.
4.2	Route of administration made prominent. Administration recommendations text relocated under compatibility section. Adult dosing no less than 4 hours apart. Elderly dosing updated.
4.3	Contraindication with apomorphine included.
4.4	Special warnings and precautions updated including myocardial ischaemia warning and admixture text relocated.
4.5	Interaction section updated with information on systemic exposure with 8mg, and information on serotonergic drugs.
4.6	Fertility comment included and Australian Pregnancy Category included.
4.7	Effects on ability to drive comment updated.
4.8	Undesirable effects updated: nervous system disorders, cardiac disorders, gastrointestinal disorders, skin and subcutaneous tissue disorders and adverse events from clinical trials.. ADR reporting URL updated.
4.9	Overdose section updated.
5.1	Clinical efficacy and safety data updated with inclusion of QT prolongation study.
5.3	Preclinical safety data relating to genotoxicity and carcinogenicity included.
6.6	Included instructions for disposal.

Please refer to the Medsafe website (www.medsafe.govt.nz) for most recent data sheet.