NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Ondansetron hydrochloride dihydrate Solution for Injection 2mg/mL.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Ondansetron Kabi injection is a clear, colourless, sterile solution. Each 1 mL of aqueous solution contains 2 mg ondansetron as the hydrochloride dihydrate. Ondansetron Kabi injection is available in ampoules ondansetron 4 mg in 2 mL or ondansetron 8 mg in 4 mL.

3. PHARMACEUTICAL FORM

Solution for Injection.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Ondansetron injection is indicated for the management 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 accordingly to the doses and combinations of chemotherapy and radiotherapy regimens used. The dose range of ondansetron should be flexible in the range of 8 to 32 mg a day and selected as indicated below. The lowest effective does should be used.

For instructions on dilution of the product before administration, see section **6.6 SPECIAL PRECAUTIONS FOR DISPOSAL.**

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, eg. 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 16 mg 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 4 mg, given by IM or slow IV injection at induction of anaesthesia.

For treatment of established post-operative nausea and vomiting, a single dose of 4 mg given by IM or slow IV injection is recommended in most patients.

Children and Adolescents

Emetogenic chemotherapy and radiotherapy (Age 6 months to 17 years)

In children with a body surface area of 0.6 to 1.2 m^2 ondansetron may be administered as a single intravenous dose of 5 mg/m^2 immediately before chemotherapy, followed by an oral dose 4 mg twelve hours later. It may be necessary to provide ongoing medication using an appropriate oral dose form (4 mg twice daily) for up to 5 days after a course of treatment.

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

Alternatively, in children aged 6 months or older, ondansetron may be administered as a single intravenous dose of 0.15 mg/kg (maximum dose 8 mg) immediately prior to chemotherapy. This dose may be repeated every 4 hours for a total of three doses. It may be necessary to provide ongoing medication using an appropriate oral dose form (4 mg 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 0.1 mg/kg up to a maximum of 4 mg either prior to, at or after induction of anaesthesia, or after surgery.

Elderly Patients:
Emetogenic chemotherapy and radiotherapy
In patients 65 to 74 years of age, the dose schedule for adults can be followed. All intravenous doses should be diluted in 50-100 mL 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 8 mg. All intravenous doses should be diluted in 50-100 mL of saline or other compatible infusion fluid and infused over 15 minutes. The initial dose of 8 mg may be followed by two further intravenous doses of 8 mg, infused over 15 minutes and given no less than four hours apart (see section **5.2 PHARMACOKINETIC PROPERTIES**).

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 PHARMACOKINETIC PROPERTIES**).

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 is required.

Impaired Hepatic Function
Clearance of ondansetron is significantly reduced and serum half-life significantly prolonged in subjects with moderate or severe impairment of hepatic function. In such patients a total daily dose of 8 mg should not be exceeded.

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.

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.

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.

Hypokalaemia and hypomagnesemia should be corrected prior to ondansetron administration.

Serotonin syndrome has been described following the concomitant use of ondansetron with other serotonergic drugs (see section **4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION**). If concomitant treatment with ondansetron and 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

4.5 INTERACTIONS 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, frusemide, 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 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

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

Phenytoin, Carbamazepine and Rifampicin
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 this drug interaction in cancer patients receiving chemotherapy is not known.

Serotonergic Drugs (e.g. SSRI's and SNRI's)
Serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) has been described following the concomitant use of ondansetron with other serotonergic drugs, including selective serotonin reuptake inhibitors (SSRI's) and serotonin noradrenaline reuptake inhibitors (SNRI's) (see section **4.4 SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE**).

Tramadol
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 15 mg/kg/day in rats had no effect on male or female fertility.

Women of childbearing potential should consider the use of contraception.

Pregnancy

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
Ondansetron is unlikely to have any effect on a person's ability to drive or operate machinery.

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.

<u>Immune System Disorders</u>

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

<u>Nervous System Disorders</u>

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.

<u>Eye Disorders</u>

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.

<u>Cardiac Disorders</u>

Uncommon:	Arrhythmias, chest pain with or without ST segment depression, bradycardia.
Rare:	QTc prolongation (including Torsade de Pointes)
Unknown:	Myocardial ischaemia

<u>Vascular Disorders</u>

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.

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

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

	Placebo (n = 548)		**Ondansetron (n = 542)**	
Total patients with AE	56%	(309)	53%	(289)
Eye disorder	16%	(86)	19%	(102)
Wound problem	13%	(72)	13%	(70)
Anxiety/agitation	7%	(36)	8%	(42)
Drowsiness/sedation	8%	(44)	6%	(34)
Nausea and/or vomiting	11%	(62)	6%	(33)
Headache	6%	(32)	6%	(32)
Pyrexia	4%	(22)	4%	(21)
Disease: lower respiratory tract	1%	(6)	3%	(16)
Arrhythmia	3%	(15)	3%	(14)

	Placebo (n = 548)		Ondansetron (n = 542)	
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 (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 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 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 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 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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 probably due to antagonism of $5HT_3$ receptors on neurons 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 8 mg and 32 mg infused intravenously over 15 minutes. At the highest tested dose of 32 mg, 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 8 mg, 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.

5.2 PHARMACOKINETIC PROPERTIES

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

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

Early Phase I studies in healthy elderly volunteers showed a slight age-related decrease in clearance, and an increase in half-life of ondansetron. However, wide inter-subject variability resulted in considerable overlap in pharmacokinetic parameters between young (< 65 years of age) and elderly subjects (≥ 65 years of age) and there were no overall differences in safety or efficacy observed between young and elderly cancer patients enrolled in CINV clinical trials to support a different dosing recommendation for the elderly.

Based on more recent ondansetron plasma concentrations and exposure-response modelling, a greater effect on QTcF is predicted in patients ≥ 75 years of age compared to young adults. Specific dosing information is provided for patients over 65 years of age and over 75 years of age for IV dosing (see section **4.2 DOSE AND METOD OF ADMINISTRATION**).

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 clinical study, 51 paediatric patients aged 1 to 24 months received either 0.1 or 0.2 mg/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 ages 5 to 24 months but comparable to 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 intravenous 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 to 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 2 mg (3 to 7 years old) or 4 mg (8 to12 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 were normalised by body weight, the values for these parameters were similar between the different age group populations. Use of weight-based dosing (0.1

mg/kg up to 4 mg 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 0.15 mg/kg intravenous 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 0.1 mg/kg or 0.2 mg/kg intravenous dose of ondansetron. Based on the population pharmacokinetic parameters for subjects aged 1 month to 48 months, administration of a 0.15 mg/kg intravenous dose of ondansetron every 4 hours for 3 doses would result in 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 to 60 mL/min), both systemic clearance and volume of distribution are reduced, resulting in a slight, but clinically insignificant, increase in elimination half-life (5.4 hours). 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 to 32 hours) 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

Sodium chloride
Citric acid monohydrate
Sodium citrate
Water for injections

6.2 INCOMPATIBILITIES

Ondansetron injection should not be administered in the same syringe or infusion as any other medication (see sections **4.2 DOSE AND METHOD OF ADMINISTRATION and 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL**).

Ondansetron injection should only be admixed with those infusion solutions which are recommended (see section **6.6 SPECIAL PRECAUTIONS FOR DISPOSAL**).

6.3 SHELF LIFE

Ondansetron Kabi ampoules have a shelf life of 4 years.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Protect from light. Store below 30°C

6.5 NATURE AND CONTENTS OF CONTAINER

As registered locally.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Ondansetron Kabi ampoule formulation is unpreserved, and should only be used on a single occasion, injected or diluted immediately after opening. Any remaining solution should be discarded.

Ondansetron Kabi injection ampoules should not be autoclaved.

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 at room temperature (below 25°C) for not more than 6 hours. The product is for single use in one patient only. Any residue should be discarded.

Compatibility with Other Drugs

Administration recommendations: slow intravenous injection (1 mg/hour) 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 160 micrograms/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 1 - 8 hours.

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

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

Compatibility with Intravenous Fluids-
In keeping with good pharmaceutical practice intravenous solutions should be prepared at the time of infusion. However, unpreserved ondansetron injection has been shown to be stable for seven days at room temperature (below 25°C) under fluorescent lighting or in a refrigerator with the following intravenous infusion fluids:

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

7. MEDICINE SCHEDULE

Prescription Only Medicine

8. SPONSOR

Fresenius Kabi New Zealand Limited
c/o GNZCC,
HSBC Tower, Level 14,
188 Quay Street, Auckland 1010, New Zealand.
Freecall: 0800 144 892

9. DATE OF FIRST APPROVAL

17 January 2014

10. DATE OF REVISION OF THE TEXT

18 March 2025

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.4	Added information on repeat dosing in paediatric patients.
4.5	Interaction section updated with information on systemic exposure with 8mg.
4.6	Fertility section updated. Added use in first trimester is not recommended.
4.8	Added AE profiles are comparable between children and adults. Myocardial Ischaema changed from Not known to Unknown. Added Xerostomia.
4.9	Overdosage section updated.
5.1	Pharmacodynamic properties section updated.
5.3	Preclinical safety data relating to genotoxicity and carcinogenicity included.