NEW ZEALAND DATA SHEET

1. PRODUCT NAME

ONDANSETRON-AFT, 4 mg ondansetron (as hydrochloride dihydrate) per 2 mL, solution for injection
ONDANSETRON-AFT, 8 mg ondansetron (as hydrochloride dihydrate) per 4 mL, solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ONDANSETRON-AFT 4 mg/2 mL solution for injection:

Each ampoule with 2 mL solution contains ondansetron hydrochloride dihydrate equivalent to 4 mg ondansetron base. Each millilitre of solution for injection contains 2.5 mg ondansetron hydrochloride dihydrate, which is equivalent to 2 mg/mL ondansetron base.

ONDANSETRON-AFT 8 mg/4 mL solution for injection:

Each ampoule with 4 mL contains ondansetron hydrochloride dihydrate equivalent to 8 mg ondansetron base. Each millilitre of solution for injection contains 2.5 mg ondansetron hydrochloride dihydrate, which is equivalent to 2 mg/mL ondansetron base.

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

3. PHARMACEUTICAL FORM

ONDANSETRON-AFT, 4 mg ondansetron (as hydrochloride dihydrate) per 2 mL, solution for injection:

A clear, colourless, sterile solution in a glass ampoule. The solution is essentially free of visible particulates. Each ampoule contains 4 mg ondansetron in 2 mL solution.
pH is 3.3 – 4.0.
Osmolarity is 270 – 320 mOsmol/kg.

ONDANSETRON-AFT, 8 mg ondansetron (as hydrochloride dihydrate) per 4 mL, solution for injection:

A clear, colourless, sterile solution in a glass ampoule. The solution is essentially free of visible particulates. Each ampoule contains 8 mg ondansetron in 4 mL solution.
pH is 3.3 – 4.0.
Osmolarity is 270 – 320 mOsmol/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ondansetron is indicated for the prevention and treatment of nausea and vomiting induced by:

- cytotoxic therapy – in adults, adolescents and children
- radiotherapy – in adults.

Ondansetron is also indicated for the prevention and treatment of post-operative nausea and vomiting in adults, adolescents and children.

4.2 Dose and method of administration

Note that other dosage forms including tablets, syrup, suppositories and wafers can be available from other brands.

DOSE

Chemotherapy and radiotherapy induced nausea and vomiting (CINV and RINV)

The emetogenic potential of cancer treatment varies according to the doses and combinations of chemotherapy and radiotherapy regimens used. The selection of dose regimen should be determined by the severity of the emetogenic challenge.

Adults

The recommended intravenous (IV) or intramuscular (IM) dose is 8 mg (administered immediately before treatment).

For highly emetogenic chemotherapy, a maximum initial dose of 16 mg IV, infused over 15 minutes, may be used. A single dose of greater than 16 mg should not be given due to dose dependent increase of QT prolongation risk (see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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

A single IV dose greater than 8 mg and up to a maximum of 16 mg must be diluted in 50 mL to 100 mL of 0.9 % sodium chloride injection or other compatible infusion fluid before administration and infused over not less than 15 minutes (see ***Method of administration***). Ondansetron doses of 8 mg or less do not need to be diluted and may be administered as a slow intramuscular or intravenous injection in not less than 30 seconds.

The initial dose of ondansetron may be followed by two additional IV or IM doses of 8 mg, given no less than 4 hours apart, or by a constant infusion of 1 mg/hour for up to 24 hours.

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

Paediatric population

In children with a body surface area of 0.6 to 1.2 m^2, ondansetron is administered as a single intravenous dose of 5 mg/m^2 immediately before chemotherapy, followed by 4 mg orally twelve hours later. Four milligrams (4 mg) orally twice daily can be continued 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 IV dose of 8 mg is administered immediately before chemotherapy, followed by 8 mg orally 12 hours later. 8 mg orally twice daily can be continued for up to five days after a course of treatment.

In children aged 6 months or older, ondansetron is administered as a single IV dose of 0.15 mg/kg (not to exceed 8 mg) immediately before chemotherapy. This dose may be repeated every four hours for a total of three doses. 4 mg orally twice daily can be continued for up to five days after a course of treatment. Adult doses must not be exceeded.

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 a 4 mg oral dose twelve hours later. 4 mg orally twice daily can be continued 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 IV dose of 8 mg is administered immediately before chemotherapy, followed by 8 mg orally 12 hours later. 8 mg orally twice daily can be continued for up to five days after a course of treatment.

Elderly population

Patients 65 years of age or older

All intravenous doses should be diluted in 50 – 100 ml of saline or other compatible infusion fluid and infused over 15 minutes and, if repeated, given no less than 4 hours apart.

Patients 65 years to 74 years of age

In patients 65 to 74 years of age, the dose schedule for adults can be followed.

Patients 75 years of age or older

The initial intravenous dose of ondansetron should not exceed 8 mg infused over 15 minutes. The initial dose of 8 mg may be followed by 2 doses of 8 mg, infused over 15 minutes and given no less than 4 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 (PONV)

Adults

For prevention of post-operative nausea and vomiting, the recommended dose of ondansetron injection is a single dose of 4 mg by intramuscular or slow intravenous injection administered at the induction of anaesthesia.

For treatment of established post-operative nausea and vomiting, a single dose of 4 mg given by intramuscular or slow intravenous injection is recommended.

Paediatric population

For prevention and treatment of PONV in paediatric patients having surgery performed under general anaesthesia, ondansetron may be administered by slow intravenous 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 population

There is limited experience in the use of ondansetron solution for injection in the prevention and treatment of post-operative nausea and vomiting in the elderly, however ondansetron is well tolerated in patients over 65 years receiving chemotherapy.

Special populations

Patients with renal impairment

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

Patients with hepatic impairment

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 oral or IV should not be exceeded.

Patients with poor sparteine/debrisoquine metabolism

The elimination half-life of ondansetron is not altered in subjects classified as poor metabolisers of sparteine and debrisoquine.

Consequently, in such patients repeat dosing will give drug exposure levels no different from those of the general population. No alteration of daily dosage or frequency of dosing is required.

METHOD OF ADMINISTRATION

ONDANSETRON-AFT is available in parenteral form only.

The formulation is unpreserved and should only be used on a single occasion, injected or diluted immediately after opening, any remaining solution should be discarded.

In keeping with good pharmaceutical practice, intravenous solutions should be prepared at the time of infusion. The solution may be administered by intravenous infusion at 1 mg/hour, e.g. from an infusion bag or syringe pump.

Compatibility with IV fluids

Compatibility studies have shown that unpreserved ondansetron injection is stable for seven days at room temperature (below 25 °C) under fluorescent lighting or in a refrigerator with the following IV infusion fluids:

- Sodium Chloride Intravenous Infusion BP 0.9% w/v
- Glucose Intravenous Infusion BP 5% w/v
- Mannitol Intravenous Infusion BP 10% w/v
- Ringer's Intravenous Infusion
- Potassium Chloride 0.3% w/v and Sodium Chloride 0.9% w/v Intravenous Infusion BP
- Potassium Chloride 0.3% w/v and Glucose 5% w/v Intravenous Infusion BP.

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

Compatibility with other drugs

Drugs that may be co-administered via the Y-site of the ondansetron giving set for ondansetron concentrations of 16 – 160 microgram/mL (e.g. 8 mg/500 mL and 8 mg/50 mL respectively) are given in **Table 1**.

Table 1: Drugs that may be co-administered with ondansetron (at 16 microgram/mL to 160 microgram/mL)* via the Y-site of the ondansetron giving set

Co-administered drugs	**Concentrations and administration rates**
Cisplatin	Concentrations up to 0.48 mg/mL cisplatin (e.g. 240 mg in 500 mL) over 1 to 8 hours.
5-Fluorouracil	Concentrations up to 0.8 mg/mL 5-fluorouracil (e.g. 2.4 g in 3 L or 400 mg in 500 mL) administered at a rate of at least 20 mL per hour (500 mL per 24 hours). The 5-fluorouracil infusion may contain up to 0.045 % w/v magnesium chloride in addition to other excipients shown to be compatible. *Note: higher concentrations of 5-fluorouracil may cause precipitation of ondansetron.*
Carboplatin	Concentrations in the range of 0.18 mg/mL to 9.9 mg/mL carboplatin (e.g. 90 mg in 500 mL to 990 mg in 100 mL), administered over 10 minutes to one hour.
Etoposide	Concentrations in the range of 0.144 mg/mL to 0.25 mg/mL etoposide (e.g. 72 mg in 500 mL to 250 mg in 1 L) administered over 30 minutes to one hour.
Ceftazidime	Doses in the range of 250 mg to 2,000 mg ceftazidime reconstituted with Water for Injections BP, as recommended by the manufacturer (e.g. 2.5 mL for 250 mg and 10 mL for 2,000 mg ceftazidime) and given as an IV bolus injection over approximately 5 minutes.
Cyclophosphamide	Doses in the range of 100 mg to 1,000 mg cyclophosphamide, reconstituted with Water for Injections BP, 5 mL per 100 mg cyclophosphamide, as recommended by the manufacturer, and given as an IV bolus injection over approximately 5 minutes.
Doxorubicin	Doses in the range of 10 mg to 100 mg reconstituted with Water for Injections BP, 5 mL per 10 mg doxorubicin, as recommended by the manufacturer and given as an IV bolus injection over approximately 5 minutes.

Co-administered drugs	Concentrations and administration rates
Dexamethasone	Dexamethasone sodium phosphate 20 mg may be administered as a slow IV injection over 2 to 5 minutes via the Y-site of an infusion set delivering 8 mg to 16 mg of ondansetron diluted in 50 mL to 100 mL of a compatible infusion fluid over approximately 15 minutes. Compatibility between dexamethasone sodium phosphate and ondansetron has been demonstrated supporting administration of these drugs through the same giving set resulting in concentrations in line of 32 micrograms to 2.5 mg/mL for dexamethasone sodium phosphate and 8 micrograms to 1 mg/mL for ondansetron.

4.3 Contraindications

Hypersensitivity to ondansetron or to any of the excipients listed in ***Section 6.1***.

Based on reports of profound hypotension and loss of consciousness when ondansetron was administered with apomorphine hydrochloride, concomitant use with apomorphine is contraindicated (see ***Section 4.5***).

4.4 Special warnings and precautions for use

Hypersensitivity

Hypersensitivity reactions have been reported in patients who have exhibited hypersensitivity to other selective 5-HT_3 receptor antagonists (serotonin antagonists). See ***Section 4.5***.

QTc interval

Ondansetron prolongs the QT interval in a dose-dependent manner (see ***Section 5.1***). 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.

Electrolyte imbalance

Hypokalaemia and hypomagnesemia should be corrected prior to ondansetron administration.

Serotonin syndrome

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.

Gastrointestinal

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

Cardiovascular:

Cases of myocardial ischemia 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 ischemia.

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, frusemide, tramadol or propofol.

Drugs affecting cytochrome P-450 enzymes

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.

QTc-prolonging drugs

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***).

Apomorphine

Based on reports of profound hypotension and loss of consciousness when ondansetron was administered with apomorphine hydrochloride, concomitant use with apomorphine is contraindicated (see ***Section 4.3***).

Phenytoin, carbamazepine, rifampicin and other strong inducers of CYP3A4

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.

The effect of these enzyme inducing agents such as carbamazepine or phenytoin on intravenous ondansetron has not been assessed. 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***).

Tramadol

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Category B1

During human epidemiological studies, an increase in orofacial clefts was observed in infants of women administered ondansetron during the first trimester of pregnancy; cardiac malformations showed conflicting results (see ***Human data***). Evaluation of experimental animal studies indicates no direct or indirect harmful effects with respect to the development of the embryo, or foetus, the course of gestation and peri- and post-natal development. However, as animal studies are not always predictive of human response the use of ondansetron in pregnancy is not recommended.

Human data

Three epidemiological studies in the US assessed the risk of specific congenital anomalies, including orofacial clefts and cardiac malformations in offspring born to mothers exposed to ondansetron during the first trimester of pregnancy.

One cohort study with 88,467 ondansetron exposed pregnancies showed an increased risk of oral clefts (3 additional cases per 10, 000 women treated, adjusted relative risk (RR), 1.24 (95% CI 1.03 – 1.48)) without an apparent increase in risk of cardiac malformations.

One case-control study using population-based birth defect registries with 23,200 cases across two datasets reported an increased risk of cleft palate in one dataset and no increased risk in the other dataset. There was no increased risk of cardiac malformations in this study.

The second case-control study found no statistically significant increase in orofacial cleft or cardiac malformations in 76,330 ondansetron exposed mothers but found an increased risk of cardiac malformations (adjusted odds ratio (OR) of 1.43 (95% CI 1.28 – 1.61)) only in a subset (5,557) of patients treated in the medical office or hospital setting.

Pregnancy testing

Pregnancy status for females of reproductive potential should be verified prior to starting the treatment with ondansetron.

Contraception

Females of reproductive potential should be advised that it is possible that ondansetron can cause harm to the developing foetus. Sexually active females of reproductive potential are recommended to use effective contraception (methods that result in less than 1% pregnancy rates) when using ondansetron during the treatment and for two days after stopping treatment with ondansetron.

Animal data

In embryo-foetal development studies in rats and rabbits, pregnant animals received oral doses of ondansetron up to 15 mg/kg/day and 30 mg/kg/day, respectively, during the period of organogenesis. With the exception of a slight decrease in maternal body weight gain in the rabbits, there were no significant effects of ondansetron on the maternal animals or the development of the offspring. At doses of 15 mg/kg/day in rats and 30 mg/kg/day in rabbits, the maternal dose was approximately 6 and 24 times the maximum recommended human oral dose of 24 mg/day, respectively, based on body surface area. In a pre- and postnatal developmental toxicity study, pregnant rats received oral doses of ondansetron up to 15 mg/kg/day from Day 17 of pregnancy to litter Day 21. With the exception of a slight reduction in maternal body weight gain, there were no effects upon the pregnant rats and the pre- and postnatal development of their offspring, including reproductive performance of the mated F1 generation. At a dose of 15 mg/kg/day in rats, the maternal dose was approximately 6 times the maximum recommended human oral dose of 24 mg/day based on BSA.

Breastfeeding

It is not known whether ondansetron is transferred into human milk. There are no data on the effects of ondansetron on the breastfed child or the effects of ondansetron on milk production. However, tests have shown that ondansetron is excreted in the milk of lactating rats. It is therefore recommended that mothers receiving ondansetron should not breast-feed their babies.

Fertility

There is no effect of ondansetron on fertility.

4.7 Effects on ability to drive and use machines

In psychomotor testing ondansetron does not impair performance nor cause sedation. No detrimental effects on such activities are predicted from the pharmacology of ondansetron.

4.8 Undesirable effects

Tabulated summary of adverse reactions

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 (≥ 1/1,000 and < 1/100)*
- *Rare (≥ 1/10,000 and < 1/1,000)*
- *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.

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*)
not known	Myocardial ischaemia

Vascular disorders

Common	Sensation of warmth or flushing
Uncommon	Hypotension

Respiratory, thoracic and mediastinal disorders

Uncommon	Hiccups

Gastrointestinal disorders

Common	Constipation

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/

4.9 Overdose

Symptoms and signs

There is limited experience of ondansetron overdose. In the majority of cases, symptoms were similar to those already reported in patients receiving the recommended doses (see ***Section 4.8***).

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.

Treatment

There is no specific antidote for ondansetron, therefore in cases of suspected overdose, symptomatic and supportive therapy should be given as appropriate.

The use of ipecacuanha to treat overdose with ondansetron is not recommended as patients are unlikely to respond due to the anti-emetic action of ondansetron itself.

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

Pharmacotherapeutic group: Serotonin (5-HT_3) antagonists, ATC code: A04AA01

Mechanism of action

Ondansetron is a potent, highly selective 5-HT_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 5-HT_3 in the small intestine initiating a vomiting reflex by activating vagal afferents via 5-HT_3 receptors. Ondansetron blocks the initiation of this reflex.

Activation of vagal afferents may also cause a release of 5-HT_3 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 5-HT_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.

Pharmacodynamic effects

Ondansetron does not alter plasma prolactin concentrations.

QT prolongation

The effect of ondansetron on the QTc interval was evaluated in a double blind, randomized, 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 pharmacokinetic properties of ondansetron are unchanged on repeat dosing.

Absorption

Equivalent systemic exposure is achieved after intramuscular and intravenous administration of ondansetron.

Distribution

The disposition of ondansetron following oral, intramuscular or intravenous dosing is similar with a steady state volume of distribution of about 140 L. Ondansetron is not highly protein bound (70 – 76%).

Metabolism

Ondansetron is cleared from the systemic circulation predominantly by hepatic metabolism through multiple enzymatic pathways. The absence of the enzyme CYP2D6 (the debrisoquine polymorphism) has no effect on ondansetron's pharmacokinetics.

Elimination

Ondansetron is cleared from the systemic circulation predominantly by hepatic metabolism. Less than 5% of the absorbed dose is excreted unchanged in the urine.

The disposition of ondansetron following oral, intramuscular or intravenous dosing is similar with a terminal elimination half-life of about 3 hours.

Characteristics in special populations

Paediatric population

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

In paediatric patients aged between 3 years 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 2 mg (3 to 7 years old or 4 mg (8 to 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 (0.1 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 428 patients (cancer patients, surgery patients and healthy volunteers), aged 1 month to 44 years following IV administration of ondansetron. Based on the analysis, systemic exposure (AUC) of ondansetron following oral or IV dosing in children and adolescents was comparable to adults, with the exception of infants aged 1 to 4 months. The volume of distribution was related to age and was lower in adults than in infants and children. Clearance was related to weight but not to age with the exception of infants aged 1 to 4 months. It is difficult to

conclude whether there was an additional reduction in clearance related to age in infants (1 to 4 months) or simply inherent variability due to the low number of subjects studied in this age group. Since patients less than 6 months of age will only receive a single dose in PONV a decreased clearance is not likely to be clinically relevant.

Elderly population

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 a 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 solution for injection dosing information is provided for patients over 65 years of age and over 75 years of age for intravenous dosing (see ***Section 4.2***).

Gender

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).

Patients with renal impairment

In patients with moderate renal impairment (creatinine clearance 15 to 60 mL/min), both systemic clearance and volume of distribution are reduced following IV administration of ondansetron, 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 following IV administration.

Patients with hepatic impairment

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

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid (for pH-adjustment)
Sodium citrate (for pH-adjustment)
Sodium chloride
Water for injections

6.2 Incompatibilities

Ondansetron injection should not be administered in the same syringe or infusion as any other medication (see ***Method of administration***).

Ondansetron injection should not be mixed with other medicines except those infusion solutions mentioned (see ***Method of administration***).

6.3 Shelf life

Unopened solution for injection:
24 months when stored below 30 °C and protected from light.

Diluted solution for injection:
7 days at room temperature (below 25 °C) under fluorescent lighting or in a refrigerator with the IV infusion fluids listed in ***Method of administration***.

6.4 Special precautions for storage

Do not freeze. Protect from light.

To reduce microbiological contamination hazards, the diluted solution should be prepared immediately prior to use and infusion commenced as soon as practicable after preparation of the mixture.

For storage conditions after dilution of the medicine, see ***Section 6.3***.

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.

Note: Preparation must be under the appropriate aseptic conditions if extended storage periods are required.

6.5 Nature and contents of container

ONDANSETRON-AFT 4 mg/per 2 mL solution for injection:
2 mL clear glass ampoules presented in packs of 1, 5 and 10 ampoules. Each ampoule contains 4 mg ondansetron in 2 mL aqueous solution.

ONDANSETRON-AFT 8 mg/4 mL solution for injection:
5 mL clear glass ampoules presented in packs of 1, 5 and 10 ampoules. Each ampoule contains 8 mg ondansetron in 4 mL aqueous solution.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

For instructions on dilution of the product before administration, see ***Method of administration***.

Ondansetron injection ampoules should not be autoclaved.

7. MEDICINE SCHEDULE

Prescription medicine

8. SPONSOR

AFT Pharmaceuticals Ltd
Level 1, 129 Hurstmere Road
Takapuna
Auckland 0622
Phone: 0800 423 823
Email: customer.service@aftpharm.com

9. DATE OF FIRST APPROVAL

19 July 2021

10. DATE OF REVISION OF THE TEXT

30 May 2024

SUMMARY TABLE OF CHANGES

Date	Section(s) Changed	Change (s)
May 2024	All Sections 4.2 4.4 4.8	Reformat consistent with new Medsafe Data Sheet Template. (v3) Update Adults and elderly population dose Include myocardial ischemia warning. Include Myocardial ischemia adverse event and updated reporting adverse event link.