Approved Professional Information for
ONDANSETRON 4 mg/2 ml FRESENIUS
ONDANSETRON 8 mg/4 ml FRESENIUS

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

ONDANSETRON 4 mg/2 ml FRESENIUS

ONDANSETRON 8 mg/4 ml FRESENIUS

Solution for injection or infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml contains ondansetron hydrochloride dihydrate equivalent to 2 mg ondansetron.

ONDANSETRON 4 mg/2 ml FRESENIUS: Each 2 ml ampoule contains 4 mg ondansetron.

ONDANSETRON 8 mg/4 ml FRESENIUS: Each 4 ml ampoule contains 8 mg ondansetron.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection or infusion.

ONDANSETRON 4 mg/2 ml FRESENIUS: Clear, colourless solution, free of any particulate matter.

ONDANSETRON 8 mg/4 ml FRESENIUS: Clear, colourless solution, free of any particulate matter.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ONDANSETRON FRESENIUS is indicated for:

- the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy
- the prevention and treatment of post-operative nausea and vomiting (PONV).

Routine prophylaxis is not recommended for patients in whom there is little expectation that nausea and vomiting will occur. The study population in all trials, thus far, consisted of mainly women undergoing laparoscopic procedures. While some men were included in some trials with similar results, clearance of the medicine is more rapid in men and insufficient numbers of men have been clinically studied to ensure certainty that efficacy and safety have been established. Few patients undergoing major abdominal surgery have been studied.

4.2 Posology and method of administration

Posology

A. CHEMOTHERAPY AND RADIOTHERAPY INDUCED NAUSEA AND VOMITING

The emetogenic potential of cancer treatment varies according to the doses and combinations of chemotherapy and radiotherapy regimens used.

Adults:

Emetogenic Chemotherapy and Radiotherapy:

For most patients receiving emetogenic chemotherapy or radiotherapy, ONDANSETRON 8 mg/4 ml FRESENIUS should be administered as a slow IV infusion (not less than 2-3 minutes) or IM injection in not less than 30 seconds, immediately before treatment.

Highly Emetogenic Chemotherapy:

A single dose of ONDANSETRON 8 mg/4 ml FRESENIUS by slow IV infusion (not less than 2-3 minutes) or IM injection in not less than 30 seconds, immediately before chemotherapy has been shown to be effective in many patients.

Higher doses may be required in some patients particularly those on high dose cisplatin and the doses should be adjusted according to the severity of the emetogenic challenge.

In these patients the following dose schedules have been shown to be effective:

A dose of 8 mg by slow IV infusion or IM injection immediately before chemotherapy, followed by two further IV or IM doses of 8 mg four hours apart, or by a constant infusion of 1 mg/hour for up to 24 hours.

OR ALTERNATIVELY:

A maximum single IV dose of 16 mg diluted in 50 - 100 ml of saline (0,9 % NaCl) or other compatible infusion fluid and infused over not less than 15 minutes immediately before chemotherapy. A single dose greater than 16 mg should not be given due to dose-dependent increased risk of QT prolongation (see section 4.4).

The efficacy of ONDANSETRON FRESENIUS in highly emetogenic chemotherapy may be enhanced by the addition of a single intravenous dose of dexamethasone phosphate 20 mg administered 30-45 minutes prior to the first ONDANSETRON FRESENIUS dose prior to chemotherapy.

Children:

Experience is limited but ONDANSETRON FRESENIUS was effective and well tolerated in children over the age of 4 years, when given intravenously at a dose of 5 mg/m^2 over 15 minutes, immediately before chemotherapy. Treatment should be continued with oral ondansetron.

Elderly patients:

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 for intravenous dosing is provided for patients over 65 years of age and over 75 years of age.

Elderly patients aged 75 years or older:

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

Adult patients aged less than 75 years:

- A single dose of intravenous ONDANSETRON FRESENIUS given for the prevention of CINV in adults (aged less than 75 years) must not exceed 16 mg (infused over at least 5 minutes).

Elderly patients aged 65 years or older:

- All intravenous doses should be diluted in 50-100 ml saline or other compatible fluid and infused over at least 15 minutes.
- Repeat intravenous doses of ONDANSETRON FRESENIUS should be given no less than 4 hours apart.

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 FRESENIUS 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.

B. PREVENTION AND TREATMENT OF POST-OPERATIVE NAUSEA AND VOMITING

Adults:

Immediately before induction of anaesthesia, or post-operatively if the patient experiences nausea and/or vomiting occurring shortly after surgery, administer 4 mg ONDANSETRON FRESENIUS undiluted intramuscularly, or if given intravenously, it must be administered by IV infusion over not less than 2 – 5 minutes or longer.

For treatment of established PONV, administration by injection is recommended.

Repeat dosing for patients who continue to experience nausea and/or vomiting post-operatively has not been studied. While recommended as a fixed dose for all, few patients above 80 kg or below 40 kg have been studied.

Children:

For prevention of post-operative nausea and vomiting in paediatric patients two years and older having surgery performed under general anaesthesia, ONDANSETRON FRESENIUS may be administered by slow intravenous infusion over 2 to 5 minutes or longer at a dose of 0,1 mg/kg up to a maximum of 4 mg either prior to, at or after induction of anaesthesia.

For the treatment of established post-operative nausea and vomiting in paediatric patients two years and older, ONDANSETRON FRESENIUS may be administered by slow intravenous infusion at a dose of 0,1 mg/kg up to a maximum of 4 mg over not less than 2-5 minutes or preferably longer.

Repeat dosing for paediatric patients who continue to experience nausea and/or vomiting has not been studied, and should thus not be given.

Elderly:

Based on 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 for intravenous dosing is provided for patients over 65 years of age and over 75 years of age.
A slight age-related decrease in clearance, and an increase in the half-life of ondansetron is predicted, presenting as slight, clinically insignificant age-related increases in both oral bioavailability (65 %) and a prolonged elimination half-life (5 hours) of ondansetron.

Patients with renal impairment:

No alteration of daily dosage or frequency of dosing is required for mild to moderate renal impairment.
There is limited information available for daily dosage or frequency of dosing for severely impaired renal function.

Patients with hepatic impairment:

Clearance of ONDANSETRON FRESENIUS 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.

Method of administration

Intramuscular injection or intravenous infusion/injection.

4.3 Contraindications

- Hypersensitivity to ondansetron or to any components of ONDANSETRON FRESENIUS (see section 6.1).
- Concomitant use with apomorphine (see section 4.5).

- ONDANSETRON FRESENIUS is contraindicated during the first 12 weeks of pregnancy irrespective of the indication, due to an increased risk of developing oral cleft palate and/or lip to the foetus (see section 4.4).
- The use of ONDANSETRON FRESENIUS for post-operative nausea and vomiting is contraindicated in pregnancy (see section 4.6).
- Congenital long QT syndrome (see section 4.4).

4.4 Special warnings and precautions for use

Cross-hypersensitivity reactions have been reported in patients who have exhibited hypersensitivity to other selective $5HT_3$ receptor antagonists.

Respiratory events should be treated symptomatically and clinicians should pay particular attention to them as precursors of hypersensitivity reactions.

ONDANSETRON FRESENIUS 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 FRESENIUS. Avoid ONDANSETRON FRESENIUS in patients with congenital long QT syndrome (see section 4.3). ONDANSETRON FRESENIUS should be administered with caution to patients who have or may develop prolongation of QTc, including patients with electrolyte abnormalities, congestive heart failure, bradydysrhythmias or patients taking other medicines that lead to QT prolongation or electrolyte abnormalities.

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.

Hypokalaemia and hypomagnesaemia should be corrected prior to ONDANSETRON FRESENIUS administration.

Post-marketing reports describe patients with serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) following the concomitant use of ONDANSETRON FRESENIUS and other serotonergic medicines (including selective serotonin reuptake inhibitors (SSRI) and serotonin noradrenaline reuptake inhibitors (SNRIs)). If concomitant treatment with ONDANSETRON FRESENIUS and other serotonergic medicines is clinically warranted, appropriate close observation of the patient is advised.

As ONDANSETRON FRESENIUS is known to increase large bowel transit time, patients with signs of intestinal obstructions should be closely monitored following administration.

In patients with adenotonsillar surgery prevention of nausea and vomiting with ONDANSETRON FRESENIUS may mask occult bleeding. Therefore, such patients should be carefully monitored after ONDANSETRON FRESENIUS.

The use of ONDANSETRON FRESENIUS during the first 12 weeks of pregnancy increases the risk of developing oral cleft palate and or lip to the foetus (see section 4.3).

Patients with hepatic impairment

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

The daily dose for children should not exceed 4 mg.

Paediatric patients receiving ONDANSETRON FRESENIUS with hepatotoxic chemotherapeutic medicines should be closely monitored for impaired hepatic function.

ONDANSETRON FRESENIUS contains sodium

ONDANSETRON FRESENIUS contains 3,35 mg sodium per ml, equivalent to 0,17 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicines and other forms of interaction

There is no evidence that ONDANSETRON FRESENIUS either induces or inhibits the metabolism of other medicines commonly co-administered with it. Specific studies have shown that there are no interactions when ONDANSETRON FRESENIUS is administered with alcohol, temazepam, furosemide, alfentanil, morphine, lidocaine, thiopental, or propofol.

Ondansetron is metabolised by multiple hepatic cytochrome P450 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 for by other enzymes and should result in little or no significant change in overall ONDANSETRON FRESENIUS clearance or dose requirement.

Caution must be exercised when ONDANSETRON FRESENIUS is co-administered with other medicines that prolong the QT interval and/or cause electrolyte abnormalities (see section 4.4).

Co-administration of ONDANSETRON FRESENIUS with QT prolonging medicines may result in additional QT-prolongation. Concomitant use of ONDANSETRON FRESENIUS with cardiotoxic medicines (e.g. anthracyclines (such as doxorubicin, daunorubicin) or trastuzumab), antibiotics (such as erythromycin), antifungals (such as ketoconazole),

antidysrhythmics (such as amiodarone) and beta blockers (such as atenolol or timolol) may increase the risk of dysrhythmias (see section 4.4).

Serotonergic medicines (e.g. SSRIs and SNRIs):

There have been post-marketing reports describing patients with serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) following the concomitant use of ONDANSETRON FRESENIUS and other serotonergic medicines (including SSRIs and SNRIs) (see section 4.4).

Apomorphine:

Cases of profound hypotension and loss of consciousness when ONDANSETRON FRESENIUS was administered concomitantly with apomorphine hydrochloride have been reported. Concomitant use of ONDANSETRON FRESENIUS and apomorphine is contraindicated as it may intensify QT-prolongation (see section 4.3).

Phenytoin, Carbamazepine and Rifampicin:

Potent inducers of the CYP3A4 isoenzyme, such as phenytoin, carbamazepine and rifampicin have been reported to increase ondansetron clearance and reduce ondansetron plasma concentrations.

Use of rifampicin or other potent inducers of the cytochrome P450 isoenzyme CYP3A4 isoenzyme, with ONDANSETRON FRESENIUS may reduce antiemetic efficacy.

Tramadol:

ONDANSETRON FRESENIUS may reduce the analgesic efficacy of tramadol.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential being treated with ONDANSETRON FRESENIUS should not become pregnant as ONDANSETRON FRESENIUS is contraindicated in the first 12 weeks of pregnancy, irrespective of the cause of the nausea and vomiting (see section 4.3).

Pregnancy

ONDANSETRON FRESENIUS is contraindicated for post-operative nausea and vomiting during pregnancy, as well as during the first 12 weeks of pregnancy irrespective of the indication, due to the risk (see section 4.3).

During the first 12 weeks of pregnancy there is an increased risk of developing oral cleft palate and/or lip in the foetus.

Women of childbearing potential to use contraception while receiving ONDANSETRON FRESENIUS and for 2 days after stopping treatment.

Lactation

Tests have shown that ONDANSETRON FRESENIUS passes into the milk of lactating animals. Mothers receiving ONDANSETRON FRESENIUS should not breastfeed their babies.

Fertility

There is no information on the effects of ONDANSETRON FRESENIUS on human fertility.

4.7 Effects on ability to drive and use machines

Patients may experience dizziness or blurred vision during treatment with ONDANSETRON FRESENIUS and are advised not to drive, use machinery or do any activity that requires alertness or clear vision.

4.8 Undesirable effects

Immune system disorders

Less frequent: Immediate hypersensitivity, including cross-sensitivity reactions sometimes severe, including anaphylaxis, bronchospasm, shortness of breath, hypotension, shock, angioedema, urticaria.

Nervous system disorders

Frequent: Headache.

Less frequent: Movement disorders (including extrapyramidal reactions such as oculogyric crisis, dystonic reactions and dyskinesia have been observed without definitive evidence of persistent clinical sequelae), seizures, dizziness during rapid intravenous administration.

Eye disorders

Less frequent: Transient visual disturbances (e.g. blurred vision) predominantly during intravenous administration, transient blindness predominantly during intravenous administration.

The majority of the blindness cases reported resolved within 20 minutes. Most patients had received chemotherapeutic medicines which included cisplatin. Some cases of transient blindness were reported as cortical in origin.

Cardiac disorders

Less frequent: Dysrhythmias, chest pain with or without ST segment depression, bradycardia, QTc prolongation (including Torsade de Pointes). Myocardial ischaemia (frequence unknown) (see section 4.4).

Vascular disorders

Frequent: Sensation of warmth or flushing.

Less frequent: Hypotension.

Respiratory, thoracic and mediastinal disorders

Less frequent: Hiccups.

Respiratory events should be treated symptomatically and clinicians should pay particular attention to them as precursors of hypersensitivity reactions.

Gastrointestinal disorders

Frequent: Constipation, increased bowel transit time.

Hepatobiliary disorders

Less frequent: Asymptomatic increases in liver function tests.

These events were commonly observed in patients receiving chemotherapy with cisplatin.

General disorders and administrative site conditions

Frequent: Pain, redness and burning at site of injection.

Reporting of suspected adverse reactions

Health care providers are asked to report any suspected adverse drug reactions to the Holder of the Certificate of Registration at the following email address: safety.fksa@fresenius-kabi.com and to the relevant medicine's regulatory authority in the country where the product is marketed.

Reporting suspected adverse reactions after authorisation of ONDANSETRON FRESENIUS is important. It allows continued monitoring of the benefit/risk balance of ONDANSETRON FRESENIUS. Health care providers are asked to report any suspected adverse reactions via the **Adverse Drug Reaction Reporting Form**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Symptoms and signs

In the majority of cases symptoms were similar to or an extension of those already reported in patients receiving recommended doses (see section 4.8). Manifestations that have been reported include visual disturbances, severe constipation, hypotension and a vasovagal episode with transient second degree AV block.

ONDANSETRON FRESENIUS prolongs the QT interval in a dose-dependent manner. ECG monitoring is recommended in cases of overdose.

Paediatric population

Paediatric cases consistent with serotonin syndrome have been reported after inadvertent oral overdoses of ondansetron (exceeded estimated ingestion of 4 mg/kg) in infants and children aged 12 months to 2 years.

Treatment

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

Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 5.10 Medicines affecting autonomic functions. Serotonin antagonists.

Pharmacotherapeutic group: Antiemetics and antinauseants, serotonin antagonists.

ATC code: A04AA01

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 medicines 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 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 cytotoxically-induced nausea and vomiting.

Ondansetron does not alter plasma prolactin concentrations.

The role of ondansetron in opiate-induced emesis is not yet established.

5.2 Pharmacokinetic properties

The disposition of ondansetron following intravenous dosing has a 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.

A 4 mg intravenous infusion of ondansetron given over 5 minutes results in peak plasma concentrations of about 65 ng/ml. Following intramuscular administration of ondansetron, peak plasma concentrations of about 25 ng/ml are attained within 10 minutes of injection.

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.

Special patient populations

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).

Children and Adolescents

Systemic exposure (AUC) of ondansetron following IV dosing in children and adolescents are comparable to adults, with the exception of infants aged 1 to 4 months. Volume is related to age and is lower in adults than in infants and children. Clearance is related to weight but not to age with the exception of infants aged 1 to 4 months. It is difficult to conclude whether there is an additional reduction in clearance related to age in infants 1 to 4 months.

Elderly

Based on 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 intravenous dosing patients over 65 years of age and over 75 years of age.

Renal impairment

In patients with renal impairment (creatinine clearance 15 – 60 ml/min), 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.

Hepatic impairment

In patients with severe hepatic impairment, systemic clearance of ondansetron is markedly reduced because of the reduced metabolism leading to prolonged elimination half-lives (15 – 32 hours) and an oral bioavailability approaching 100 %.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride, citric acid monohydrate (for pH-adjustment), sodium citrate dihydrate (for pH-adjustment) and water for injections.

6.2 Incompatibilities

NOTE: As a general principle it is not recommended to mix medicines for infusion.

ONDANSETRON FRESENIUS should not be administered in the same syringe or infusion as any other medication.

ONDANSETRON FRESENIUS ampoules should not be autoclaved.

ONDANSETRON FRESENIUS should only be admixed with those infusion solutions which are recommended (see section 6.6).

6.3 Shelf life

Unopened: 48 months.

After opening: The product should be used immediately.

Diluted solutions: If the diluted solutions are not used immediately, they should be stored at 2 – 8 °C for not longer than 7 days.

6.4 Special precautions for storage

Store at or below 30 °C.

Keep the ampoules in the outer container in order to protect from light.

For storage of the diluted solutions, see section 6.3.

6.5 Nature and contents of container

ONDANSETRON 4 mg/2 ml FRESENIUS: 2 ml clear glass ampoule packed in cartons of 1's, 5's or 10's.

ONDANSETRON 8 mg/4 ml FRESENIUS: 5 ml clear glass ampoule packed in cartons of 1's, 5's or 10's.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Instructions for handling

Inspect visually prior to use. Only clear solutions without particles should be used.

For single use only. Discard any unused portion.

Compatibility with intravenous fluids

Intravenous solutions should be prepared at the time of infusion. However, ONDANSETRON FRESENIUS 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 Intravenous Infusion 0,9 % *m/v*.
- Glucose Intravenous Infusion 5 % *m/v*.
- Ringers Intravenous Infusion.
- Potassium Chloride 0,3 % *m/v* and Sodium Chloride 0,9 % *m/v* Intravenous Infusion.
- Potassium Chloride 0,3 % *m/v* and Glucose 5 % *m/v* Intravenous Infusion.

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. Dilution of ONDANSETRON FRESENIUS in sodium chloride 0,9 % *m/v* or in glucose 5 % *m/v* have been demonstrated to be stable in polypropylene syringes. It is considered that ONDANSETRON FRESENIUS 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.

Compatibility with other medicines

ONDANSETRON FRESENIUS may be administered by intravenous infusion at 1 mg/hour, e.g. from an infusion bag or syringe pump. The following medicines may be administered via the Y-site of the ONDANSETRON FRESENIUS giving set for ondansetron concentrations of 16 to 160 micrograms/ml (e.g. 8 mg/500 ml and 8 mg/50 ml respectively).

Cisplatin:

Concentrations up to 0,48 mg/ml (e.g. 240 mg in 500 ml) administered over one to eight hours.

Dexamethasone:

Dexamethasone sodium phosphate 20 mg may be administered as a slow intravenous injection over 2 - 5 minutes via the Y-site of an infusion set delivering 8 mg of

ONDANSETRON FRESENIUS diluted in 50 - 100 ml of a compatible infusion fluid over approximately 15 minutes. Compatibility between dexamethasone sodium phosphate and ONDANSETRON FRESENIUS has been demonstrated supporting administration of these medicines through the same giving set with resulting in-line concentrations in the ranges of 32 µg - 2,5 mg/ml for dexamethasone sodium phosphate and 8 µg – 1 mg/ml for ONDANSETRON FRESENIUS.

5-Fluorouracil:

Concentrations up to 0,8 mg/ml (e.g. 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 5-fluorouracil infusion may cause precipitation of ONDANSETRON FRESENIUS. The 5-fluorouracil infusion may contain up to 0,045 % *m/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 (e.g. 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 (e.g. 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 2 000 mg reconstituted with Water for Injections, as recommended by the manufacturer (e.g. 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, 5 ml per 100 mg cyclophosphamide, as recommended by the manufacturer, and given as an intravenous bolus injection over approximately five minutes.

Doxorubicin:

Doses in the range 10 - 100 mg reconstituted with Water for Injections, 5 ml per 10 mg

doxorubicin, as recommended by the manufacturer, and given as an intravenous bolus injection over approximately five minutes.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Fresenius Kabi South Africa (Pty) Ltd

Stand 7, Growthpoint Business Park

162 Tonetti Street

Halfway House, Midrand, 1685

South Africa

8. REGISTRATION NUMBER

ONDANSETRON 4 mg/2 ml FRESENIUS: 43/5.10/0542

ONDANSETRON 8 mg/4 ml FRESENIUS: 43/5.10/0543

9. DATE OF FIRST AUTHORISATION

27 July 2012

10. DATE OF REVISION OF THE TEXT

08 June 2023