SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

ONDANSETRON 4 mg/2 ml BIOTECH

ONDANSETRON 8 mg/4 ml BIOTECH

Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ONDANSETRON 4 mg/2 ml BIOTECH:

Each 2 ml ampoule contains ondansetron 4 mg (as hydrochloride dihydrate) for intramuscular or intravenous administration.

ONDANSETRON 8 mg/4 ml BIOTECH:

Each 4 ml ampoule contains ondansetron 8 mg (as hydrochloride dihydrate) for intramuscular or intravenous administration.

Sugar free.

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Injection, for intramuscular (IM) or slow intravenous (IV) administration.

A clear, colourless solution, practically free from visible particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ONDANSETRON BIOTECH 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 agent 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

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.

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

Adults:

Emetogenic chemotherapy and radiotherapy:

For most patients receiving emetogenic chemotherapy or radiotherapy, ONDANSETRON 8 mg/4 ml BIOTECH 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 BIOTECH 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 sections 4.4).

The efficacy of ONDANSETRON BIOTECH 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 BIOTECH dose prior to chemotherapy.

Children:

Experience is currently limited, but ONDANSETRON BIOTECH 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 cancer chemotherapy.

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 BIOTECH 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 BIOTECH 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 BIOTECH 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 BIOTECH 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 and therefore parenteral or oral administration is recommended.

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 BIOTECH 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 BIOTECH 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 BIOTECH may be administered by slow intravenous infusion at a dose of 0,1 mg/kg up to 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 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.

A slight age-related decrease in clearance, and an increase in the half-life of ONDANSETRON BIOTECH 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 BIOTECH.

Patients with renal/hepatic impairment:

Patients with renal impairment:

No alteration of daily dosage or frequency of dosing, or route of administration is required for mild or moderate renal impairment.

There is limited information available for daily dosage or frequency of dosing, or route of administration for severe renal impairment.

Patients with hepatic impairment:

Clearance of ONDANSETRON BIOTECH 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.

Method of administration

Intramuscular injection or intravenous infusion/injection.

4.3 Contraindications

Hypersensitivity to ondansetron or to any components of ONDANSETRON BIOTECH (see section 6.1).

Concomitant use with apomorphine (see section 4.5).

ONDANSETRON BIOTECH use 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 BIOTECH for post-operative nausea and vomiting is contraindicated in pregnancy (see section 4.6).

Congenital long QT syndrome.

4.4 Special warnings and precautions for use

Cross-hypersensitivity reactions have been reported in patients who have exhibited hypersensitivity to other

selective 5HT3 receptor antagonists.

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

ONDANSETRON BIOTECH 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 BIOTECH. Avoid ONDANSETRON BIOTECH in patients with congenital long QT syndrome (see section 4.3). ONDANSETRON BIOTECH 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 medicinal products 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 BIOTECH administration.

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

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

In patients with adeno-tonsillar surgery, prevention of nausea and vomiting with ONDANSETRON BIOTECH may mask occult bleeding. Therefore, such patients should be carefully monitored after ONDANSETRON BIOTECH.

The use of ONDANSETRON BIOTECH 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 BIOTECH 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.

The daily dose for children should not exceed 4 mg.

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

ONDANSETRON BIOTECH contains less than 1 mmol sodium (23 mg) per 4 ml ampoule (3,56 mg per ml), that is to say essentially “sodium free”.

4.5 Interaction with other medicines and other forms of interaction

There is no evidence that ONDANSETRON BIOTECH 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 BIOTECH is administered with alcohol, temazepam, furosemide, alfentanil, morphine, lidocaine, thiopental, 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 BIOTECH is co-administered with other medicines that prolong the QT interval and/or cause electrolyte abnormalities (see section 4.4).

Co-administration of ONDANSETRON BIOTECH with QT prolonging medicines may result in additional QT prolongation. Concomitant use of ONDANSETRON BIOTECH with cardiotoxic medicines (e.g., anthracyclines (such as doxorubicin, daunorubicin) or trastuzumab), antibiotics (such as erythromycin), antifungals (such as ketoconazole), antiarrhythmics (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 BIOTECH and other serotonergic medicines (including SSRIs and SNRIs) (see section 4.4)

Apomorphine: Based on reports of profound hypotension and loss of consciousness when ONDANSETRON BIOTECH was administered with apomorphine hydrochloride, concomitant use with apomorphine is contraindicated (see section 4.3).

Tramadol: ONDANSETRON BIOTECH may reduce the analgesic effect of tramadol.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

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

Pregnancy

ONDANSETRON BIOTECH 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 of developing oral cleft palate and/or lip to the foetus (see section 4.3).

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

Breastfeeding

ONDANSETRON BIOTECH passes into the milk of lactating animals. Mothers receiving ONDANSETRON BIOTECH should not breastfeed their babies.

Fertility

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

4.7 Effects on ability to drive and use machines

ONDANSETRON BIOTECH causes nervous system and eye disorders which may adversely affect the ability of patients to drive or operate machines. Patients on treatment with ONDANSETRON BIOTECH should therefore not drive or use machines until the effects of ONDANSETRON BIOTECH treatment are known (see section 4.8).

4.8 Undesirable effects

Adverse events are listed below by system organ class and frequency.

The following frequencies are estimated at the standard recommended doses of ONDANSETRON BIOTECH. The adverse event profiles in children and adolescents were comparable to those seen in adults.

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:	Seizures, movement disorders (including extrapyramidal reactions such as dystonic reactions, oculogyric crisis and dyskinesia have been observed without definitive evidence of persistent clinical sequelae). 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).

Frequency unknown:	Myocardial ischemia (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 medical practitioners should pay particular attention to them as precursors of hypersensitivity reactions.	
Gastrointestinal disorders:	
Frequent:	Constipation, increased bowel transit time.
Hepato-biliary disorders:	
Less frequent:	Asymptomatic increases in liver function tests.
These events were frequently observed in patients receiving cancer chemotherapy with cisplatin.	
General disorders and administration site conditions:	
Frequent:	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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the **"6.04 Adverse Drug Reactions 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 the 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 prolongs the QT interval in a dose-dependent manner. ECG monitoring is recommended in cases of overdose.

Treatment

There is no specific antidote for ondansetron. In all cases of suspected overdose, treatment is symptomatic and supportive as appropriate.

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

5. PHARMACOLOGICAL PROPERTIES

Pharmacological classification: A 5.10 Medicines affecting autonomic functions. Serotonin antagonists

ATC code: A04AA01

5.1 Pharmacodynamic properties

Mechanism of Action:

Ondansetron is a potent, highly selective 5-HT_3 receptor-antagonist. Ondansetron's actual mechanism of action in the control of nausea and vomiting is unknown. Chemotherapeutic agents and radiotherapy may cause release of 5-HT in the small intestine, initiating a vomiting reflex by activating vagal afferents via 5-HT_3 receptors. The initiation of this reflex is blocked by ondansetron. Activation of vagal afferents may also cause a release of 5-HT 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 the antagonism of 5-HT_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

Following oral administration, ondansetron is passively and completely absorbed from the gastrointestinal tract and undergoes first pass metabolism. Peak plasma concentrations of about 30 ng/ml are attained approximately 1.5 hours after an 8 mg dose. For doses above 8 mg the increase in ondansetron systemic exposure with dose is greater than proportional; this may reflect some reduction in first pass metabolism at higher oral doses. Mean bioavailability in healthy male subjects, following the oral administration of a single 8 mg tablet, is approximately 55 to 60 %.

Bioavailability, following oral administration, is slightly enhanced by the presence of food but unaffected by antacids.

Studies in healthy elderly volunteers have shown slight, but clinically insignificant, age-related increases in oral bioavailability (65 %). Elimination half-life was (5 hours) of ondansetron.

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

In paediatric patients aged 1 to 4 months (n = 19) undergoing surgery, weight normalised clearance was approximately 30 % slower than in patients aged 5 to 24 months (n = 22) but comparable to the patients aged 3 to 12 years. The half-life in the patient population aged 1 to 4 months 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. The differences in pharmacokinetic parameters in the 1 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 medicines like ondansetron.

In paediatric patients aged 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 (3-7 years old) or 4 mg (8-12 years old) were reduced. The magnitude of the change was age-related, with clearance falling from about 300 ml/min at 12 years of age to 100 ml/min at 3 years. Volume of distribution fell from about 75 L at 12 years to 17 L at 3 years. 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 age-related changes and is effective in normalising systemic exposure in paediatric patients.

Elderly

Early Phase I studies in healthy elderly volunteers showed a slight age-related decrease in clearance, and an increase in half-life of ondansetron.

Other studies in healthy elderly volunteers showed slight, clinically insignificant age-related increases in both oral bioavailability (65 %) and a prolonged elimination half-life (5 hours) of ondansetron.

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.

Renal Impairment

In patients with renal impairment (creatinine clearance 15-60 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.

Hepatic Impairment

In patients with severe hepatic impairment, systemic clearance of ondansetron is markedly reduced because of reduced pre-systemic 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

Sodium citrate dihydrate

Citric acid monohydrate

Water for injections

6.2 Incompatibilities

ONDANSETRON BIOTECH injection should not be administered in the same syringe or infusion as any other medication. ONDANSETRON BIOTECH should only be mixed with those infusion solutions that are recommended (see section 6.6).

6.3 Shelf life

24 months (unopened).

24 hours (dilutions stored 2 - 8 °C).

6.4 Special precautions for storage

Store below 25 °C.

Protect from light.

6.5 Nature and contents of container

ONDANSETRON 4 mg/ 2 ml BIOTECH:

2 ml clear glass ampoules (5 ampoules packed into a carton).

ONDANSETRON 8 mg/ 4 ml BIOTECH:

4 ml clear glass ampoules (5 ampoules packed into a carton).

6.6 Special precautions for disposal and other handling

Compatibility with intravenous fluids:

ONDANSETRON BIOTECH injection should only be admixed with those infusion solutions which are recommended.

Intravenous solutions should be prepared at the time of infusion.

ONDANSETRON BIOTECH injection has been shown to be stable for seven days at room temperature under fluorescent lighting or in a refrigerator with the following intravenous infusion fluids:

5 % glucose solution;

0,9 % sodium chloride solution;

10 % mannitol solution or

Ringers solution.

Compatibility studies have been undertaken in polyethylene bags and in clear glass vials.

It is considered that ONDANSETRON BIOTECH 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.

Compatibility with other medicines:

NOTE: It is not recommended to mix medicines for infusion.

ONDANSETRON BIOTECH injection 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 BIOTECH 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 BIOTECH diluted in 50-100 ml of a compatible infusion fluid over approximately 15 minutes. Compatibility between dexamethasone sodium phosphate and ONDANSETRON BIOTECH 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 BIOTECH.

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 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 10 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 Injection BP, 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 Injection BP, 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 to 100 mg, reconstituted with water for injection BP, 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

Biotech Laboratories (Pty) Ltd.

Ground Floor, Block K West, Central Park

400 16th Road, Randjespark

Midrand

1685

8. REGISTRATION NUMBER(S)

ONDANSETRON 4 mg/2 ml BIOTECH: 38/5.10/0200

ONDANSETRON 8 mg/4 ml BIOTECH: 38/5.10/0217

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 07 April 2006

10. DATE OF REVISION OF THE TEXT

11 January 2024