APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

EMISTOP 4 mg solution for injection.

EMISTOP 8 mg solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

EMISTOP 4 mg: Each 2 mL ampoule contains ondansetron hydrochloride dihydrate equivalent to 4 mg ondansetron (2 mg/mL).

EMISTOP 8 mg: Each 4 mL ampoule contains ondansetron hydrochloride dihydrate equivalent to 8 mg ondansetron (2 mg/mL).

EMISTOP is sugar-free.

EMISTOP contains 9 mg of sodium per mL (see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

EMISTOP 4 mg injection: A clear and colourless solution, free from visible particles.

EMISTOP 8 mg injection: A clear and colourless solution, free from visible particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

EMISTOP is indicated for the management of nausea and vomiting induced by chemotherapy and radiotherapy.

EMISTOP is also indicated for the prevention and treatment of post-operative nausea and vomiting.
Routine prophylaxis is not recommended for patients in whom there is little expectation that nausea and vomiting will occur.

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.

Adults:

Emetogenic chemotherapy and radiotherapy:

For most patients receiving emetogenic chemotherapy and radiotherapy, EMISTOP 8 mg 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, followed by 8 mg orally twelve-hourly. In circumstances where delayed or prolonged emesis is expected after 24 hours, ondansetron may be continued orally, 8 mg twice daily for up to 5 days after a course of treatment.

Highly emetogenic chemotherapy:

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

OR

- a single dose of 16 mg diluted in 50 – 100 mL of saline or other compatible infusion fluid, 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 EMISTOP 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 EMISTOP dose prior to chemotherapy.

To protect against delayed or prolonged emesis after the first 24 hours, ondansetron may be continued orally, 8 mg twice daily for up to 5 days after a course of treatment.

Special populations

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 below for patients over 65 years of age and over 75 years of age.

- ***In patients 75 years of age or older***, the initial intravenous dose of EMISTOP, given for the prevention of chemotherapy-induced nausea and vomiting (CINV) should not exceed 8 mg, (infused over at least 15 minutes).
- ***In patients aged less than 75 years***, a single dose of intravenous EMISTOP 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 of saline or other compatible infusion fluid (see section 6.6) and infused over 15 minutes. The initial dose of 8 mg may be followed by two further intravenous doses of 8 mg, infused over 15 minutes and given no less than four hours apart. (see section 5.2).

Paediatric population

Experience is currently limited, but EMISTOP 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, followed by oral therapy of doses of ondansetron 4 mg every 12 hours for up to 5 days.

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 EMISTOP 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 EMISTOP 4 mg undiluted intramuscularly or intravenously. If given intravenously, it must be administered by IV infusion over not less than 2 – 5 minutes or longer.

Alternatively, for the prevention of post-operative nausea and vomiting, ondansetron may be given orally one hour prior to induction of anaesthesia.

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.

Special populations

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 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.

Paediatric population

For prevention of post-operative nausea and vomiting in paediatric patients two years and older having surgery performed under general anaesthesia, EMISTOP 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 patients two years and older, EMISTOP may be administered by slow intravenous injection 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 patients who continue to experience nausea and/or vomiting post-operatively has not been studied and thus should not be given.

Patients with renal/hepatic impairment:

Patients with renal impairment:

No alteration of daily dosage or frequency of dosing, or route of administration is required. There is limited information for daily dosage or frequency of dosing, or route of administration for severe renal

impairment.

Patients with hepatic impairment:

Clearance of EMISTOP 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.

4.3 Contraindications

- hypersensitivity to ondansetron or to any of the ingredients of EMISTOP (see section 6.1)
- pregnancy
- ondansetron use is contraindicated during the first 12 weeks of pregnancy irrespective of the indication (see sections 4.4 and 4.6)
- congenital long QT syndrome
- concomitant use with apomorphine (see section 4.5).

4.4 Special warnings and precautions for use

Myocardial Ischaemia:

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 with hepatic impairment:

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

EMISTOP prolongs QT interval in a dose-dependent manner. In addition, cases of Torsade de Pointes have been reported. Avoid EMISTOP in patients with congenital long QT syndrome (see section 4.3). EMISTOP should be administered with caution in 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.
Hypokalaemia and hypomagnesaemia should be corrected prior to EMISTOP administration.

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

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

Patients with signs of sub-acute intestinal obstructions should be monitored following administration, as EMISTOP is known to increase large bowel transit time.

Serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) been reported following the concomitant use of EMISTOP and other serotonergic medicines [including selective serotonin reuptake inhibitors (SSRI) and serotonin noradrenaline reuptake inhibitors (SNRIs)]. Appropriate observation of the patient is advised if the concomitant treatment with EMISTOP and other serotonergic medicines is warranted.

Prevention of nausea and vomiting with EMISTOP may mask occult bleeding in patients with adenotonsillar surgery. Therefore, such patients should be followed carefully after EMISTOP administration.

The use of ondansetron during the first 12 weeks of pregnancy increases the risk of developing oral cleft palate and/or lip to the foetus.

Sodium:

EMISTOP contains 3,6 mg, 14,4 mg and 57,6 mg sodium per 1 mL, 4 mL and 16 mL, respectively, equivalent to 0,18 %, 0,72 % and 2,88 % of the WHO recommended maximum daily intake of 2 g sodium for an

adult.

Paediatric population

Close monitoring is required for paediatric patients receiving EMISTOP with hepatotoxic chemotherapeutic medicines as concomitant use may cause impaired hepatic function.

CINV:

When calculating the dose on a mg/kg basis and administering three doses at 4-hour intervals, the total daily dose will be higher than if one single dose of 5 mg/m^2 followed by an oral dose is given.
The comparative efficacy of these two different dosing regimens has not been investigated in clinical trials.
Cross-trial comparison indicates similar efficacy for both regimens.

4.5 Interaction with other medicines and other forms of interaction

Cases of profound hypotension and loss of consciousness have been reported with the concomitant use of apomorphine and EMISTOP.
Concomitant use with apomorphine is therefore contraindicated (see section 4.3).
Concomitant use of apomorphine and EMISTOP may intensify QT prolongation (see sections 4.3 and 4.4).

Potent inducers of isoenzyme CYP3A4, such as phenytoin,

carbamazepine and rifampicin have been reported to increase ondansetron clearance and reduce ondansetron plasma concentrations.

Efficacy of tramadol is reduced in patients using EMISTOP.

Co-administration of EMISTOP with hepatic cytochrome P-450 enzymes such as CYP3A4, CYP2D6 and CYP1A2 metabolise EMISTOP. 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 EMISTOP is co-administered with medicines that prolong the QT interval and/or cause electrolyte abnormalities (see section 4.4).

Use of EMISTOP with QT prolonging medicines may result in additional QT prolongation. The risk of arrythmias may be increased with concomitant use of EMISTOP 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) (see section 4.4).

Serotonergic Medicines (SSRI and SNRIs)

Serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) has been reported with concomitant use of EMISTOP with other serotonergic medicines (including SSRIs and SNRIs).

Specific studies have shown that there are no interactions when EMISTOP is administered with alcohol, temazepam, furosemide, alfentanil, tramadol, morphine, lidocaine, thiopental, or propofol.

There is no evidence that EMISTOP either induces or inhibits the metabolism of other medicines commonly co-administered with it.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

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

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

Pregnancy

EMISTOP 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 can be associated with an increased risk of developing oral cleft palate and/or lip to the foetus.

Breastfeeding

Tests have shown that ondansetron passes into the milk of lactating animals.
It is therefore recommended that mothers receiving EMISTOP should not breastfeed their babies.

Fertility

There is not information on the effects of EMISTOP on human fertility.

4.7 Effects on ability to drive and use machines

EMISTOP has no or negligible influence on the ability to drive and use machines.
No signs of sedation or impairment of performance, when using machinery during psychomotor testing, were observed for EMISTOP, however, impaired vision and dizziness are possible side effects therefore patients should not drive or use machines until the effects of EPISTOP treatment are known (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The following frequencies are estimated at the standard recommended doses of ondansetron.

The adverse event profiles in children and adolescents were comparable to that seen in adults.

Tabulated list of adverse effects

System Organ Class	Frequency	Side effects
Immune system disorders	Less frequent	Severe hypersensitivity reactions (e.g. anaphylaxis, bronchospasm, shortness of breath, hypotension, shock, angioedema)
Nervous system disorders	Frequent Less frequent	Headache Seizures, dizziness, movement disorders (including extrapyramidal reactions such as oculogyric crisis, dystonic reactions and dyskinesia)
Eye disorders	Less frequent	Transient visual disturbances (e.g. blurred vision), transient blindness (during intravenous administration), oculogyric crisis

Cardiac disorders	Less frequent Frequency unknown	Dysrhythmias, tachycardia, bradycardia and chest pain with or without ST segment depression, QTc prolongation (including Torsade de Pointes), dysrhythmias, cardiopulmonary arrest, atrial fibrillation Myocardial ischaemia
Vascular disorders	Frequent Less frequent	Sensation of warmth or flushing Hypotension
Respiratory, thoracic and mediastinal disorders	Less frequent	Hiccups, laryngeal oedema and laryngospasm
Gastrointestinal disorders	Frequent	Constipation, diarrhoea, abdominal pain or stomach cramps, increased bowel transit time
Hepatobiliary disorders	Less frequent	Transient asymptomatic increases in aminotransferases and in liver function tests
General disorders and administrative site conditions	Frequent	Pain, redness and burning at site of injection, rash, urticaria, syncope

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 requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-

umc.org) found on the SAHPRA website.

An email can be sent directly to the company, pharmacovigilance@pharmadynamics.co.za, to ensure safety of the product.

4.9 Overdose

Signs and symptoms:

Manifestations that have been reported include severe constipation, visual disturbances, hypotension and vasovagal episode with transient second-degree AV block.

Management of overdose:

In case of suspected overdose, symptomatic and supportive therapy should be given as appropriate, as there is no specific antidote for ondansetron.

Ondansetron prolongs QT interval in a dose-dependent manner.

ECG monitoring is recommended in case of overdosage.

Paediatric population

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiemetics and antinauseants

ATC code: A04AA01

Pharmacological classification: A 5.10 Medicines affecting autonomic functions, serotonin antagonists.

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 medicines 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 nausea and vomiting induced by chemotherapy and radiotherapy may be due to

antagonism of 5-HT_3 receptors on neurons located both in peripheral and central nervous system. In psychomotor testing, ondansetron does not cause sedation nor impair performance.

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

Absorption:

Plasma prolactin concentrations are not altered by ondansetron.

Ondansetron is absorbed following oral administration, with maximum plasma concentrations of about 30 nanogram /mL being attained approximately 1,6 hours after an 8 mg dose. The absolute oral bioavailability of ondansetron is approximately 60 %.

Distribution:

The disposition of ondansetron following both intravenous and oral dosing is similar with a terminal elimination half-life of about 3 hours and a steady state volume of distribution of about 140 litres. Plasma protein binding is 70 – 76 %. Equivalent systemic exposure is achieved after intramuscular and intravenous administration of ondansetron.

Elimination:

Ondansetron is cleared from systemic circulation predominantly by hepatic metabolism through multiple enzymatic pathways, with less than 5 % of a dose excreted unchanged in the urine. Studies in healthy elderly volunteers have shown a prolonged elimination half-life (5 hours) and slightly increased bioavailability (65 %) for ondansetron. 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.

Pharmacokinetics in special patient groups

Hepatic impairment:

As a result of reduced pre-systemic metabolism in patients with severe hepatic impairment, the systemic clearance of ondansetron is markedly reduced with prolonged elimination half-lives (15 – 32 hours) and an oral bioavailability approaching 100 %.

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).

Elderly:

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 to support a different dosing recommendation for the elderly.

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

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 following intravenous administration.

Paediatric population

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 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 compensates for age- related changes and is effective in normalising systemic exposure in paediatric patients.

Based on analysis in various patient groups (cancer patients, surgery patients and healthy volunteers) following intravenous administration of ondansetron, systemic exposure (AUC) of ondansetron following oral or IV dosing in children and adolescents was comparable to adults.

Volume was related to age and was lower in adults than children.

Clearance was related to weight but not to age.

5.3 Preclinical safety data

No additional data of relevance.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid monohydrate

Sodium chloride

Sodium citrate

Water for injection

6.2 Incompatibilities

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

6.3 Shelf life

36 months.

6.4 Special precautions for storage

For single use only. Discard any unused portion.

Store at or below 30 °C. Keep well closed. Protect from light.

Do not refrigerate or freeze.

6.5 Nature and contents of container

EMISTOP 4 mg: is packed into a 2 mL clear and colourless type I glass ampoule with a blue dot. Each ampoule contains 2 mL solution for injection. 5 ampoules are packed into an outer carton.

EMISTOP 8 mg: is packed into a 5 mL clear and colourless type I glass ampoule with a blue dot. Each ampoule contains 4 mL solution for injection. 5 ampoules are packed into an outer carton.

6.6 Special precautions for disposal and other handling

Instructions for handling:

EMISTOP injection should not be administered in the same syringe or infusion as any other medicine. EMISTOP injection ampoules should not be autoclaved.

Compatibility with intravenous fluids:

EMISTOP solution for injection should only be admixed with those infusion solutions which are recommended. Prepare intravenous solutions at the time of infusion and use immediately after admixing.

EMISTOP solution for injection is compatible with the below-listed intravenous infusion fluids.

Although chemically and physically stable, from a microbiological view, solutions should not be stored for longer than 24 hours at a temperature of 2 ºC – 8 ºC unless prepared under controlled aseptic conditions.

- 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.

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Compatibility with other medicines:

Note: As a general rule, it is not recommended to mix medicines for infusion.

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 EMISTOP diluted in 50 – 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 medicines through the same giving set, with resulting in-line concentrations in the ranges of 32 micrograms – 2,5 mg/mL for dexamethasone sodium phosphate and 8 micrograms – 1 mg/mL for ondansetron.

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 EMISTOP. 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 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 30 minutes to one hour.

Ceftazidime: Doses in the range 250 mg to 2000 mg reconstituted with water for injection, 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, 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 mg to 100 mg, reconstituted with Water for Injection, 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 THE CERTIFICATE OF REGISTRATION

Pharma Dynamics (Pty) Ltd

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Tel: +27 21 707 7000

or 0860-PHARMA (742 762)

8. REGISTRATION NUMBER(S)

EMISTOP 4 mg: A45/5.10/0386

EMISTOP 8 mg: A45/5.10/0387

All strengths are not necessarily marketed.

9. DATE OF FIRST AUTHORISATION

Date of registration: 31 July 2014

10. DATE OF REVISION OF THE TEXT

16 February 2026

NAMIBIA

EMISTOP 4 mg: NS2 15/5.10/0178

EMISTOP 8 mg: NS2 15/5.10/0179

ZAMBIA

EMISTOP 4 mg: POM 051/016

EMISTOP 8 mg: POM 051/017