**PROFESSIONAL INFORMATION**

**EMISTOP RANGE**

**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

Injection (aqueous solution).

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 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 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 (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:**

Efficacy and tolerance in patients aged over 65 years was similar to that seen in younger adults indicating no need to alter dosage or route of administration in the elderly.

In patients 75 years of age or older, the initial intravenous dose of EMISTOP should not exceed 8 mg. 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.

**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 in not less than 30 seconds, preferably over 2 – 5 minutes.

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:**

Safety and efficacy have not been established with the use of EMISTOP in the prevention and treatment of post-operative nausea and vomiting in the elderly.

**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 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.

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 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.

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.

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

**Special populations**

**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 available on severely impaired renal or hepatic function.

***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
- pregnancy
- ondansetron use is contraindicated during the first 12 weeks of pregnancy irrespective of the indication
- 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.

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.

As ondansetron is known to increase large bowel transit time, patients with signs of sub-acute intestinal obstruction should be monitored following administration of EMISTOP.

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 sodium. To be taken into consideration for patients on a controlled sodium diet.

**Paediatric population**

Close monitoring is required for paediatric patients receiving EMISTOP with hepatotoxic chemotherapeutic medicines as concomitant use may course 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 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).

*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**

**Pregnancy**

Safety in pregnancy has not been established (see section 4.3).

**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:**

No signs of sedation or impairment of performance, when using machinery during psychomotor testing, were observed for EMISTOP.

**4.8 Undesirable effects**

**a. 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.

**b.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<br>Less frequent | Headache<br>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<br><br><br><br><br><br><br>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<br>Myocardial ischaemia |

| | | |
|---|---|---|
| Vascular disorders | Frequent<br>Less frequent | Sensation of warmth or flushing<br>Hypotension |

| | | |
|---|---|---|
| Respiratory, thoracic and mediastinal disorders | Less frequent | Hiccups, laryngeal oedema and laryngospasm |
| Gastrointestinal disorders | Frequent | Constipation, diarrhoea, abdominal pain or stomach cramps |
| Hepato-biliary 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 asked to report any suspected adverse reactions to SAHPRA via the online service for adverse drug reaction reporting by following the link: https://www.sahpra.org.za/Publications/Index/8.

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 selective 5-$HT_3$ receptor antagonist.

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.

**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 ng/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 %.

**Elimination:**

Ondansetron is cleared from systemic circulation predominantly by metabolism 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.

**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 citrate

Sodium chloride

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**

**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.

***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 µg – 2,5 mg/mL for dexamethasone sodium phosphate and 8 µg – 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 CERTIFICATE OF REGISTRATION

Pharma Dynamics (Pty) Ltd

1st Floor, Grapevine House

Steenberg Office Park

Silverwood Close

Westlake, Cape Town

7945, South Africa

## 8. REGISTRATION NUMBERS

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/RENEWAL OF THE AUTHORISATION

Date of registration: 31 July 2014

## 10. DATE OF REVISION OF THE TEXT

23 November 2022

**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