PROFESSIONAL INFORMATION

SCHEDULING STATUS **S4**

1 NAME OF THE MEDICINE

NAUSETRON 4 mg INJECTION

NAUSETRON 8 mg INJECTION

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

NAUSETRON 4 mg INJECTION: Ampoules containing ondansetron 4 mg (as hydrochloride dihydrate) in 2 mL aqueous solution for intramuscular or intravenous administration.

NAUSETRON 8 mg INJECTION: Ampoules containing ondansetron 8 mg (as hydrochloride dihydrate) in 4 mL aqueous solution for intramuscular or intravenous administration.

Excipient(s) with known effect:

Sugar content: Sugar free

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Injection

Clear glass ampoules containing a colourless solution free of visible particulate matter.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

NAUSETRON is also indicated for the prevention and treatment of postoperative 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

Posology

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, **NAUSETRON** 8 mg should be administered as a slow IV (in not less than 30 seconds) or IM injection immediately before treatment.

Highly emetogenic chemotherapy:

A single dose of **NAUSETRON** 8 mg by slow IV (in not less than 30 seconds) or IM injection immediately before chemotherapy has been shown to be effective in many patients.

Higher doses may be required in some patients, particularly those on high doses of cisplatin, and the doses of **NAUSETRON** 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 (in not less than 30 seconds) or IM injection immediately before chemotherapy, followed by two further IV (in not less than 30 seconds) 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 to 100 mL of 0,9 % sodium chloride 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 increase of QT prolongation risk (see section 4.4.)

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

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

Children:

Experience is currently limited, but **NAUSETRON** 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 ondansetron therapy, at doses of 4 mg every 12 hours for up to 5 days.

Elderly patients:

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.

NAUSETRON causes a dose-dependent prolongation of the corrected QT interval (QTc) of the electrocardiogram (ECG), which can lead to *Torsade de Pointes*, a potentially life-threatening heart dysrhythmia (see section 4.4). Therefore, the following dose restrictions are in place for use of intravenous **NAUSETRON**:

In elderly patients, 75 years of age or older, a single dose of IV **NAUSETRON** given for the prevention of chemotherapy-induced nausea and vomiting (CINV) should not exceed 8 mg (infused over at least 15 minutes). Repeat intravenous doses of **NAUSETRON** should be given not less than 4 hours apart. All IV doses should be diluted in 50 to 100 mL of 0,9 % *m/v* sodium chloride solution, or other compatible infusion fluid, and infused over 15 minutes.

In elderly patients, aged 65 years to 74 years, the dose schedule for CINV in adults can be followed. A single dose of intravenous **NAUSETRON** given for CINV in adults should not exceed 16 mg. All IV doses should be diluted in 50 to 100 mL of 0,9 % *m/v* sodium chloride solution or other compatible infusion fluid and infused over 15 minutes.

Prevention and treatment of postoperative nausea and vomiting:

Adults:

Immediately before induction of anaesthesia, or postoperatively if the patient experiences nausea and/or vomiting occurring shortly after surgery, administer 4 mg **NAUSETRON** undiluted intramuscularly or intravenously. If given intravenously, it should be administered in not less than 30 seconds, preferably over 2 to 5 minutes.

Repeat dosing for patients who continue to experience nausea and/or vomiting postoperatively 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 postoperative nausea and vomiting in paediatric patients 2 years and older, having surgery performed under general anaesthesia, **NAUSETRON** 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 postoperative nausea and vomiting in paediatric patients 2 years and older, **NAUSETRON** may be administered by slow intravenous injection at a dose of 0,1 mg/kg up to a maximum of 4 mg.

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

Elderly:

Safety and efficacy have not been established with the use of **NAUSETRON** in the prevention and treatment of postoperative nausea and vomiting in the elderly.

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 impairment.

Patients with hepatic impairment: Clearance of **NAUSETRON** 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 (see section 4.4).

Method of administration

NAUSETRON injection may be administered intramuscularly or intravenously.

For precautions to be taken before manipulating or administering the product, refer to section 6.6.

For instructions on dilution of the medicine before administration, see section 6.6

4.3 Contraindications

- **NAUSETRON** is contraindicated in patients known to have hypersensitivity to ondansetron or any of the ingredients of **NAUSETRON**
- The use of ondansetron for postoperative nausea and vomiting is contraindicated in pregnancy and lactation (see section 4.6)
- Concomitant use with apomorphine (see section 4.5)
- Congenital long QT syndrome
- Concomitant use with medicines prolonging the QT interval (see section 4.5).

4.4 Special warnings and precautions for use

In patients with moderate or severe impairment of hepatic function, clearance of **NAUSETRON** is significantly reduced and serum half-life significantly prolonged. In such patients, a total daily dose of 8 mg should not be exceeded (see section 4.2).

NAUSETRON prolongs the QT interval in a dose-dependent manner. ECG changes including QT interval prolongation and cases of *Torsades de Pointes* have been reported in patients receiving **NAUSETRON**. **NAUSETRON** should be administered with caution to patients who

have or may develop prolongation of QTc. These conditions include patients with electrolyte abnormalities, congestive heart failure, bradydysrhythmias, or patients taking other medicines that lower the heart rate, or electrolyte abnormalities. Patients should be assessed for risk factors for QT prolongation or *Torsade de Pointes* before **NAUSETRON** is prescribed. Hypokalaemia and hypomagnesaemia should also be corrected prior to **NAUSETRON** administration.

Cases of myocardial ischaemia have been reported in patients treated with serotonin receptor antagonists. In some patients, especially in the case of intravenous administration, symptoms appeared immediately after administration of serotonin receptor antagonist (e.g. **NAUSETRON**). Patients should be alerted to the signs and symptoms of myocardial ischaemia.

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 containing medicines (such as NAUSETRON) and other serotonergic medicines, including selective serotonin reuptake inhibitors (SSRIs) and serotonin noradrenaline reuptake inhibitors (SNRIs) (see section 4.5). If concomitant treatment with **NAUSETRON** and other serotonergic medicines is clinically justified, appropriate monitoring of the patient is advised.

Cross-hypersensitivity reactions have been reported in patients who previously exhibited hypersensitivity to other selective 5-HT_3 receptor antagonists, e.g. granisetron or dolasetron. Respiratory events should be treated symptomatically and should be given particular attention as they may be precursors to hypersensitivity reactions.

Patients with signs of subacute intestinal obstructions should be monitored following administration, as **NAUSETRON** is known to delay large bowel transit time and cause

constipation.

Sodium content

NAUSETRON contains 3,6 mg of sodium (as sodium citrate and sodium chloride) per mL, which should be taken into consideration for patients on a sodium-restricted diet.

4.5 Interaction with other medicines and other forms of interaction

Apomorphine*:* Profound hypotension and loss of consciousness have been reported when ondansetron was administered with apomorphine hydrochloride. Concomitant use with apomorphine is contraindicated (see section 4.3).

Serotonergics*:* Serotonin syndrome has been reported following the concomitant use of **NAUSETRON** and other serotonergic medicines (including SSRIs and SNRIs) (see section 4.4).

NAUSETRON should not be co-administered with other medicines that prolong the QT interval and/or cause electrolyte abnormalities (see section 4.3 and 4.4).

Concomitant use of **NAUSETRON** with cardiotoxic medicines (e.g. anthracyclines such as doxorubicin, daunorubicin or trastuzumab), antibiotics (such as erythromycin) or antifungals (such as ketoconazole), antidysrhythmic medicines (such as amiodarone) and beta-blockers (such as atenolol or timolol) may increase the risk of dysrhythmias.

Tramadol*:* Ondansetron may reduce the analgesic effect of tramadol.

***Enzyme inhibitors**:* The active ingredient of NAUSETRON, 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 usually compensated by other enzymes.

Enzyme inducers: In some patients, potent inducers of CYP3A4 (e.g. phenytoin, carbamazepine and rifampicin) may increase the oral clearance of ondansetron and decrease ondansetron blood concentrations.

4.6 Fertility, pregnancy and lactation

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

Lactation: Ondansetron passes into the milk of lactating animals. Mothers receiving **NAUSETRON** should not breastfeed their babies.

4.7 Effects on ability to drive and use machines

NAUSETRON may have an influence on ability to drive or use machines. **NAUSETRON** may cause dizziness, movement disorders and transient visual problems (see section 4.8).

4.8 Undesirable effects

a. Summary of the safety profile

Not applicable

b. Tabulated list of adverse reactions

Immune system disorders

Less frequent: Immediate hypersensitivity reactions, bronchospasm, hypotension, dyspnoea, shock, anaphylaxis, angioedema, urticaria

Psychiatric disorders

Less frequent: Depression

Nervous system disorders

Frequent: Headache

Less frequent: Movement disorders including extrapyramidal reactions such as dystonic reactions, oculogyric crisis, seizures, dizziness during or shortly after rapid IV administration and dyskinesia **NOTE 1**

Eye disorders

Less frequent: Transient visual disturbances (e.g. blurred vision), transient blindness **NOTE 2**

Cardiac disorders

Less frequent: Dysrhythmia, bradycardia, chest pain with or without ST segment depression, ECG changes including QTc prolongation (including *Torsade de Pointes*)

Frequency unknown: Myocardial ischaemia (see section 4.4)

Vascular disorders

Frequent: Sensation of warmth or flushing

Less frequent: Hypotension

Respiratory, thoracic and mediastinal disorders

Less frequent: Hiccups

Gastrointestinal disorders

Frequent: Delay in large bowel transit time, constipation

Hepatobiliary disorders

Less frequent: Asymptomatic increases in liver function tests [NOTE 3]

Skin and subcutaneous tissue disorders

Less frequent: Rashes, urticaria

General disorders and administration site conditions

Frequent: Local IV injection site reactions - pain, redness, burning

c. Description of selected adverse reactions

NOTES:

1. Observed without definitive evidence of persistent clinical sequelae.
2. It is reported that the majority of the blindness cases resolved within 20 minutes. Most patients had received chemotherapeutic medicines, which included cisplatin. Some cases of transient blindness were reported as cortical in origin.
3. Frequently observed in patients receiving chemotherapy with cisplatin.

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 providers

are asked to report any suspected adverse drug reactions to SAHPRA via the **"6.04 Adverse Drug Reaction Reporting Form"**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8. By reporting side effects, you can help provide more information on the safety of **NAUSETRON**.

4.9 Overdose

See section 4.8. Manifestations that have been reported include severe constipation, visual disturbances, hypotension and vasovagal episode with transient second-degree AV block. In cases 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 cases of overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group and ATC code: Antiemetics and antinauseants, serotonin (5HT3) antagonists, ATC code: A04AA01.

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 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.

Ondansetron causes a dose-dependent prolongation of the corrected QT interval (QTc) of the electrocardiogram, which can lead to *Torsade de Pointes* – a potentially life-threatening heart dysrhythmia (see section 4.2 and section 4.4).

5.2 Pharmacokinetic properties

The disposition of ondansetron following intravenous dosing has a terminal half-life of about 3 hours and a steady-state volume of distribution of about 140 L. Plasma protein binding is 70 to 76 %. Ondansetron is predominantly cleared from the systemic circulation by metabolism, with less than 5 % of a dose excreted unchanged in the urine.

Ondansetron has a prolonged elimination half-life (5 hours) and increased bioavailability (65 %) in the elderly.

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 to 32 hours).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid, sodium citrate, sodium chloride, water for injection.

6.2 Incompatibilities

This medicine must not be mixed with other medicines except those mentioned in section 6.6.

6.3 Shelf life

36 months.

After opening: **NAUSETRON** ampoules are unpreserved and should only be used on a single occasion and injected or diluted immediately after opening.

6.4 Special precautions for storage

Store at or below 30 ˚C. Protect from light.

KEEP ALL MEDICINES OUT OF REACH OF CHILDREN.

For storage conditions after first opening of the medicine, see section 6.3.

6.5 Nature and contents of container

NAUSETRON 4 mg INJECTION: Carton containing 5 clear glass ampoules.

NAUSETRON 8 mg INJECTION: Carton containing 5 clear glass ampoules.

6.6 Special precautions for disposal and other handling

Instructions for handling injections:

NAUSETRON ampoules are unpreserved and should only be used on a single occasion and injected or diluted immediately after opening. Any remaining solution should be discarded.

NOTE: Preparation of **NAUSETRON** infusions should be under the appropriate aseptic conditions**.**

NAUSETRON injection ampoules should not be autoclaved.

Compatibility with intravenous fluids:

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

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

In keeping with good pharmaceutical practice, intravenous solutions should be prepared at the time of infusion. However, **NAUSETRON** injection 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*
- Ringer's 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. Dilutions of **NAUSETRON** 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 **NAUSETRON** injection diluted with other compatible infusion fluids would be stable in polypropylene syringes.

Compatibility with other medicines:

NAUSETRON should not be administered in the same syringe or infusion as any other medicine, except where compatibility has been demonstrated (see below).

NAUSETRON 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 **NAUSETRON** giving set for ondansetron concentrations of 16 to 160 µg/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 1 to 8 hours.

Dexamethasone: Dexamethasone sodium phosphate 20 mg may be administered as a slow intravenous injection over 2 to 5 minutes via the Y-site of an infusion set delivering 8 mg of **NAUSETRON** diluted in 50 to 100 mL of a compatible infusion fluid over approximately 15 minutes. Compatibility between dexamethasone sodium phosphate and **NAUSETRON** has been demonstrated supporting administration of these medicines through the same giving set, with resulting in-line concentrations in the ranges of 32 µg to 2,5 mg/mL for dexamethasone sodium phosphate and 8 µg to 1 mg/mL for **NAUSETRON**.

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 1 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 1 hour.

Ceftazidime: Doses in the range 250 mg to 2 000 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 5 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 5 minutes.

Doxorubicin: Doses in the range 10 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 5 minutes.

7 HOLDER OF CERTIFICATE OF REGISTRATION

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8 REGISTRATION NUMBERS

NAUSETRON 4 mg INJECTION: A39/5.10/0462

NAUSETRON 8 mg INJECTION: A39/5.10/0463

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 20 June 2005

10 DATE OF REVISION OF THE TEXT

31 October 2024

PI 31 October 2024