1.3.1.1 [1]PROPOSED PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

1 NAME OF THE MEDICINE

PALONOSETRON 0,05 mg/mL FRESENIUS 250 microgram/5 mL solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of solution contains 50 micrograms palonosetron (as hydrochloride). Each single-dose vial of 5 mL or pre-filled injection of 5 mL of solution contains 250 micrograms palonosetron (as hydrochloride).

Excipients with known effect

Each vial or pre-filled syringe contains less than 1 mmol sodium (23 mg) (see section 4.4).

Contains mannitol. Each 5 mL syringe or 5 mL vial contains 202,4 mg mannitol (i.e. 40,48 mg/mL).

For the full list of excipients, see section 6.1.

[1] The annotated PI, v3.0, appears in module 1.5.5.1. This PI complies with the Clinical Evaluation recommendations of 13 January 2022.

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3 PHARMACEUTICAL FORM

Solution for injection

Clear, essentially colourless solution, free from visible particles.

pH: 4,7 – 5,3

Osmolality: 270 – 330 mOsmol/kg

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

PALONOSETRON FRESENIUS is indicated for:

- the prevention of acute nausea and vomiting associated with highly emetogenic cancer chemotherapy and
- the prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy.

4.2 Posology and method of administration

Posology

Use in adults

250 micrograms palonosetron, administered as a single intravenous bolus, approximately 30 minutes before the start of chemotherapy. PALONOSETRON FRESENIUS should be injected over 30 seconds.

Repeated dosing of PALONOSETRON FRESENIUS within a seven-day interval is not recommended.

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The efficacy of palonosetron as in PALONOSETRON FRESENIUS in the prevention of nausea and vomiting induced by highly emetogenic chemotherapy may be enhanced by the addition of a corticosteroid administered prior to chemotherapy.

Use in children and adolescents

Use in patients under 18 years of age is not recommended until further data becomes available.

Use in elderly

No dosage adjustment is necessary in the elderly.

Use in patients with renal impairment

No dosage adjustment is necessary for patients with impaired renal function.

No data is available for patients with end stage renal disease undergoing haemodialysis.

Use in patients with hepatic impairment

No dosage adjustment is necessary for patients with impaired hepatic function.

Method of administration

For intravenous use.

Single use only, any unused solution should be discarded.

See section 6.6 for instructions for use.

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4.3 Contraindications

- Hypersensitivity to palonosetron or to any of the excipients of PALONOSETRON FRESENIUS (see section 6.1).

4.4 Special warnings and precautions for use

PALONOSETRON FRESENIUS should not be used to prevent or treat nausea and vomiting in the days following chemotherapy, if not associated with another chemotherapy administration.

Serotonin syndrome

There have been reports of serotonin syndrome with the use of 5-HT_3 antagonists (such as PALONOSETRON FRESENIUS), either alone or in combination with other serotonergic medicines such as SSRIs (selective serotonin reuptake inhibitors) and SNRIs (serotonin noradrenaline reuptake inhibitors). Appropriate observation of patients for serotonin syndrome-like symptoms is advised.

Constipation/obstipation

PALONOSETRON FRESENIUS may increase large bowel transit time. Faecal impaction requiring hospitalisation have been reported in association with a dose of 750 µg palonosetron as in PALONOSETRON FRESENIUS. Patients with a history of constipation or signs of sub-acute intestinal obstruction should be monitored following administration.

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Cardiac effects

At all dose levels tested, palonosetron as in PALONOSETRON FRESENIUS did not induce clinically relevant prolongation of the QTc interval. However, as with other 5-HT3 antagonists, caution should be exercised in the concomitant use of PALONOSETRON FRESENIUS with medicines that increase the QT interval, or in patients who have, or are likely to develop, prolongation of the QT interval:

- with a personal or family history of QT prolongation,
- with bradydysrhythmia,
- with conduction disturbances,
- with electrolyte abnormalities,
- with congestive heart failure,
- taking medicines that increase the QT interval,
- taking anti-dysrhythmic medicines, or
- taking other medicines that lead to electrolyte abnormalities.

Hypokalaemia and hypomagnesemia should be corrected prior to PALONOSETRON FRESENIUS administration.

Excipients

PALONOSETRON FRESENIUS contains less than 1 mmol sodium (23 mg) per vial, i.e. essentially 'sodium- free'.

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4.5 Interactions with other medicines and other forms of interaction

Palonosetron is mainly metabolised by CYP2D6, with minor contribution by CYP3A4 and CYP1A2 isoenzymes. Based on *in vitro* studies, palonosetron as in PALONOSETRON FRESENIUS does not inhibit or induce cytochrome P450 isoenzymes at clinically relevant concentrations.

Serotonergic medicines

There have been reports of serotonin syndrome following concomitant use of 5-HT3 antagonists and other serotonergic medicines (including SSRIs and SNRIs).

Chemotherapeutic medicines

In pre-clinical studies, palonosetron as in PALONOSETRON FRESENIUS did not inhibit the anti-tumour activity of the five chemotherapeutic medicines tested (cisplatin, cyclophosphamide, cytarabine, doxorubicin and mitomycin C).

Metoclopramide

In a clinical study, no significant pharmacokinetic interaction has been demonstrated between palonosetron and steady state concentration of oral metoclopramide, which is a CYP2D6 inhibitor.

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CYP2D6 inducers and inhibitors:

In a population pharmacokinetic analysis, it has been shown that there was no significant effect on palonosetron clearance when co-administered with CYP2D6 inducers (dexamethasone and rifampicin) and inhibitors (including amiodarone, celecoxib, chlorpromazine, cimetidine, doxorubicin, fluoxetine, haloperidol, paroxetine, quinidine, ranitidine, ritonavir, sertraline or terbinafine).

Corticosteroids

Palonosetron has been administered safely with corticosteroids.

Other medicines

Palonosetron as in PALONOSETRON FRESENIUS has been administered safely with analgesics, anti-emetic/anti-nauseants, antispasmodics and anticholinergic medicines.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is no experience of palonosetron in human pregnancy. PALONOSETRON FRESENIUS should therefore not be used in pregnant women.

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Breastfeeding

Since there is no data concerning excretion of palonosetron in breastmilk, breastfeeding should be discontinued during therapy with PALONOSETRON FRESENIUS.

4.7 Effects on the ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

Since palonosetron as in PALONOSETRON FRESENIUS may induce dizziness, somnolence or fatigue, patients should be cautioned when driving or operating machines.

4.8 Undesirable effects

Summary of the safety profile

In clinical studies at a dose of 250 micrograms the most frequently observed adverse reactions, at least possibly related to palonosetron as in PALONOSETRON FRESENIUS, were headache and constipation.

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Tabulated list of adverse events

System organ class/ Frequency	Adverse reactions
Immune system disorders	
Less frequent:	Hypersensitivity, anaphylaxis, anaphylactic/anaphylactoid reactions and shock
Metabolism and nutrition disorders	
Less frequent:	Hyperkalaemia, metabolic disorders, hypocalcaemia, hypokalaemia, anorexia, hyperglycaemia, decreased appetite
Psychiatric disorders	
Less frequent:	Anxiety, euphoric mood
Nervous system disorders	
Frequent:	Headache, dizziness
Less frequent:	Somnolence, insomnia, paraesthesia, hypersomnia, peripheral sensory neuropathy
Eye disorders	
Less frequent:	Eye irritation, amblyopia
Ear and labyrinth disorders	
Less frequent:	Motion sickness, tinnitus

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Cardiac disorders

Less frequent: Tachycardia, bradycardia, extrasystoles, myocardial ischaemia, sinus tachycardia, sinus arrhythmia, supraventricular extrasystoles , electrocardiogram QT prolonged

Vascular disorders

Less frequent: Hypotension, hypertension, vein discolouration, vein distended

Respiratory, thoracic and mediastinal disorders

Less frequent: Hiccups

Gastrointestinal disorders

Frequent: Constipation, diarrhoea

Less frequent: Dyspepsia, abdominal pain, upper abdominal pain, dry mouth, flatulence

Hepato-biliary disorders

Less frequent: Hyperbilirubinaemia, elevated transaminases

Skin and subcutaneous tissue disorders

Less frequent: Allergic dermatitis, pruritic rash

Musculoskeletal and connective tissue disorders

Less frequent: Arthralgia

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Renal and urinary disorders	
Less frequent:	Urinary retention, glycosuria
General disorders and administration site conditions	
Less frequent:	Asthenia, pyrexia, fatigue, feeling hot, influenza like illness
Frequency unknown:	Injection site reactions (burning, induration, discomfort and pain).

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 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

No case of overdose has been reported.

Doses of up to 6 mg have been used in clinical trials. The highest dose group showed a similar incidence of adverse events compared to the other dose groups and no dose response effects were observed.

In the unlikely event of an overdose with PALONOSETRON FRESENIUS, this should be managed with supportive care. Dialysis

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studies have not been performed, however, due to the large volume of distribution, dialysis is unlikely to be an effective treatment for palonosetron overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 5.10 Serotonin antagonists

Pharmacotherapeutic group: Antiemetics and antinauseants, serotonin ($5HT_3$) antagonists. ATC code: A04AA05

Palonosetron is a potent and selective serotonin subtype 3 ($5\text{-}HT_3$) receptor antagonist with a strong binding affinity for this receptor – both *in vitro* and *in vivo*. Palonosetron has little or no affinity for other bioreceptors, including other serotonergic receptors ($5\text{-}HT_1$, $5\text{-}HT_2$ and $5\text{-}HT_4$).

The major human metabolites, M9 and M4, have only marginal clinically non-relevant activity.

5.2 Pharmacokinetic properties

Absorption

Following intravenous administration, an initial decline in plasma concentrations is followed by slow elimination from the body with a mean terminal elimination half-life of approximately 2 days [40 hours]. Mean

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maximum plasma concentration (C_{max}) and area under the concentration-time curve (AUC0-∞) are generally dose-proportional over the dose range of 0,3 – 90 µg/kg in healthy persons and in cancer patients.

Distribution

Palonosetron at the recommended dose is widely distributed in the body with a volume of distribution of approximately 6,9 to 7,9 L/kg. Approximately 62 % of palonosetron is bound to plasma proteins.

Biotransformation

Palonosetron is eliminated by dual routes, about 40 % is eliminated through the kidney and with approximately 50 % metabolised to form two primary metabolites, M9 and M4, which have less than 1 % of the 5-HT_3 receptor antagonist activity of palonosetron.

In vitro metabolism studies have shown that CYP2D6 and to a lesser extent, CYP3A4 and CYP1A2 isoenzymes are involved in the metabolism of palonosetron. However, clinical pharmacokinetic parameters are not significantly different between poor and extensive metabolisers of CYP2D6 substrates. Palonosetron does not inhibit or induce cytochrome P450 isoenzymes at clinically relevant concentrations.

Elimination

After a single intravenous dose of 10 microgram/kg [^{14}C]-palonosetron, approximately 80 % of the dose was recovered within 144 hours in the

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urine, with palonosetron representing approximately 40 % of the administered dose, as unchanged active substance.

After a single intravenous bolus administration in healthy subjects the total body clearance of palonosetron is 173 ± 73 mL/min and renal clearance was 53 ± 29 mL/min. The low total body clearance and large volume of distribution resulted in a terminal elimination half-life in plasma of approximately 40 hours. Ten percent of patients have a mean terminal elimination half-life greater than 100 hours.

Pharmacokinetics in special patient groups

Elderly patients

Age does not affect the pharmacokinetics of palonosetron. No dosage adjustment is necessary in elderly patients.

Gender

Gender does not affect the pharmacokinetics of palonosetron. No dosage adjustment is necessary based on gender.

Paediatric patients

No pharmacokinetic data are available in patients below 18 years of age.

Renal impairment

Mild to moderate renal impairment does not significantly affect palonosetron pharmacokinetic parameters.

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Severe renal impairment reduces renal clearance, however, total body clearance in these patients is similar to healthy persons. No dosage adjustment is required in patients with renal insufficiency.

No pharmacokinetic data in haemodialysis patients are available.

Hepatic impairment

Hepatic impairment does not significantly affect total body clearance of palonosetron compared to healthy persons. While the terminal elimination half-life and mean systemic exposure of palonosetron is increased in patients with severe hepatic impairment, this does not warrant dose reduction.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (E421)

Disodium edetate dihydrate

Sodium citrate dihydrate (E331)

Citric acid anhydrous (E330)

Sodium hydroxide (pH adjustment)

Hydrochloric acid (pH adjustment)

Water for injections

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6.2 Incompatibilities

PALONOSETRON FRESENIUS must not be mixed with other medicines.

6.3 Shelf life

3 years.

Upon opening of the vial or syringe, use immediately and discard any unused solution.

6.4 Special precautions for storage

Store at or below 30 °C. Do not refrigerate. Keep in cartons to protect from light.

Any unused solution should be discarded.

6.5 Nature and contents of container

PALONOSETRON 0,05 mg/mL FRESENIUS is supplied in 5 mL pre-filled syringes or 5 mL single-dose vials:

- Pre-filled plastic syringes composed of a barrel of cyclo olefin copolymer material and a plunger and tip cap of halobutyl rubber, packed in a carton.

  It is available in packs of 1 or 10 pre-filled syringes.
- Type I glass vials 6RB BB, closed with a halobutyl rubber stopper which is fixed into its position by an aluminium-plastic cap.

It is available in packs of 1 or 10 vials or 1 or 10 pre-filled syringes.

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Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Single use only, any unused solution should be discarded.

Any unused product or waste material should be disposed of in accordance with local requirements.

Application of pre-filled syringes:

Sterility must be ensured. The outer surface of the syringe and the plunger rod are not sterile.

1) Take out the syringe from the packaging
2) Remove the tip cap from the syringe and connect the infusion line, needle or cannula to the syringe. Get rid of the air bubble (a small bubble can remain) and the ready-to-use syringe will be administered manually.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Fresenius Kabi South Africa (Pty) Ltd
Stand 7 Growthpoint Business Park
162 Tonetti street
Halfway House, Midrand 1685
SOUTH AFRICA

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8 REGISTRATION NUMBER

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 DATE OF REVISION OF THE TEXT

15 March 2022