PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

CHEMSENTRON 50 µg/ml solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution contains 50 micrograms palonosetron (as hydrochloride).

Each vial of 5 ml of solution contains 250 micrograms palonosetron (as hydrochloride).

For full list of excipients, see section 6.1.

Sugar free.

3 PHARMACEUTICAL FORM

Solution for injection.

Clear, essentially colourless solution free from evidence of contamination.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

CHEMSENTRON 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

Adults

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

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

The efficacy of CHEMSENTRON 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.

Special populations

Elderly

No dosage adjustment is necessary in the elderly.

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 hemodialysis.

Hepatic impairment

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

Paediatric population

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

Method of administration

For intravenous use.

Single use only, any unused solution should be discarded.

4.3 Contraindications

Hypersensitivity to palonosetron or to any of the excipients of CHEMSENTRON (see section 6.1).

4.4 Special warnings and precautions for use

As palonosetron may increase large bowel transit time, patients with a history of constipation or signs of sub-acute intestinal obstruction should be monitored following administration. Two cases of constipation with faecal impaction requiring hospitalisation have been reported in association with palonosetron 750 micrograms.

At all dose levels tested, palonosetron did not induce clinically relevant prolongation of the QTc interval.

However, caution should be exercised in the concomitant use of palonosetron with medicines that increase the QT interval or in patients who have or are likely to develop prolongation of the QT interval.

These conditions include patients with a personal or family history of QT prolongation, electrolyte abnormalities, congestive heart failure, bradydysrhythmia, conduction disturbances and in patients taking anti-dysrhythmic medicines or other medicines that lead to QT prolongation or electrolyte abnormalities. Hypokalaemia and hypomagnesemia should be corrected prior to 5-HT_3-antagonist administration.

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

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

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

4.5 Interaction 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 does not inhibit or induce cytochrome P450 isoenzymes at clinically relevant concentrations.

Chemotherapeutic medicines

In preclinical studies, palonosetron 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 was shown between a single intravenous dose of palonosetron and steady state concentration of oral metoclopramide, which is a CYP2D6 inhibitor.

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.

Serotonergic medicines (e.g. SSRIs and SNRIs)

There have been reports of serotonin syndrome following concomitant use of 5-HT_3 antagonists and other serotonergic medicines (including SSRIs and SNRIs).

Other medicines

Palonosetron has been administered safely with analgesics, anti-emetic/ anti-nauseants, antispasmodics and anti-cholinergic medicines.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Breastfeeding

Since there is no data concerning excretion of palonosetron in breast milk, breastfeeding should be discontinued during therapy.

Fertility

There are no data concerning the effect of palonosetron on fertility.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Since CHEMSENTRON may include dizziness, somnolence or fatigue, patients should be cautioned when driving or operating machines.

4.8 Undesirable effects

a. Summary of the safety profile

The most frequently reported adverse reactions are headache and constipation.

b. Tabulated summary of adverse reactions

MedDRA 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, anorexia, hyperglycaemia, decreased appetite, hypokalaemia
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
Cardiac disorders	Less frequent	Tachycardia, bradycardia, extrasystoles, myocardial ischaemia, sinus tachycardia, sinus dysrhythmia, supraventricular extrasystoles

MedDRA System Organ Class	Frequency	Adverse reactions
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	Hyperbilirubinemia
Skin and subcutaneous tissue disorders	Less frequent	Dermatitis allergic, pruritic rash
Musculoskeletal, connective tissue and bone disorders	Less frequent	Arthralgia
Renal and urinary disorders	Less frequent	Urinary retention, glycosuria
General disorders and administrative site conditions	Less frequent	Asthenia, pyrexia, fatigue, feeling hot, influenza like illness, injection site reactions (burning, induration, discomfort and pain)
Investigations	Less frequent	Elevated transaminases, electrocardiogram QT prolonged

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 "**6.04 Adverse Drug Reactions & Quality Problem 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 overdose with CHEMSENTRON, this should be managed with supportive care. Dialysis studies have not been performed, however, due to the large volume of distribution; dialysis is unlikely to be an effective treatment for CHEMSENTRON overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A.5.10 Serotonin antagonists

Pharmacotherapeutic group: Antiemetics and anti-nauseants, 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. 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 maximum plasma concentration (C_{max}) and area under the concentration- time curve ($AUC_{0-\infty}$) are generally dose-proportional over the dose range of 0,3 to 90 µg/kg in healthy subjects 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.

Metabolism

Palonosetron is eliminated by dual route, about 40 % 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 micrograms/ kg [^{14}C]-palonosetron, approximately 80 % of the dose was recovered within 144 hours in the 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 was 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

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.

Renal impairment

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

Severe renal impairment reduces renal clearance, however, total body clearance in these patients is similar to healthy subjects. No dosage adjustment is necessary in patients with renal insufficiency. No pharmacokinetic data in hemodialysis patients are available.

Hepatic impairment

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

Paediatric population

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid monohydrate (E330)

Disodium edetate

Hydrochloric acid solution (for pH adjustment) (E507)

Mannitol (E421)

Sodium citrate (E331)

Sodium hydroxide solution (for pH adjustment) (E524)

Water for injection

6.2 Incompatibilities

CHEMSENTRON must not be mixed with other medicines.

6.3 Shelf life

5 years.

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

6.4 Special precautions for storage

Store at or below 25 °C.

CHEMSENTRON does not require any special storage conditions.

6.5 Nature and contents of container

CHEMSENTRON is supplied in a glass vial with rubber stopper and aluminium cap. It is

available in packs of 1 vial containing 5 ml of solution.

6.6 Special precautions for disposal

Single use only, any unused solution should be discarded.

There are no special requirements for the disposal of unused product or waste material.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Kahma Biotech (Pty) Ltd

106, 16th Road

Midrand

8 REGISTRATION NUMBER

550344

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 DATE OF REVISION OF THE TEXT