Approved Professional Information for Medicines for Human Use:

KEMOPREV IV

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

KEMOPREV IV SOLUTION FOR INJECTION

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

KEMOPREV IV solution for injection

Each 1 mL of solution contains 50 micrograms palonosetron (as palonosetron hydrochloride).

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

Contains sugar (D-Mannitol)

Each 1 mL of KEMOPREV IV solution for injection contains 41,5 mg D-Mannitol per mL.

Each KEMOPREV IV solution for injection contains 207,5 mg D-Mannitol per vial.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

KEMOPREV IV solution for injection

Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

KEMOPREV IV 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. KEMOPREV IV should be injected over 30 seconds.

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

The efficacy of KEMOPREV IV 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 population

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 haemodialysis.

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

KEMOPREV IV is for intravenous use.

4.3 Contraindications

KEMOPREV IV is contraindicated in:

Hypersensitivity to palonosetron hydrochloride or to any of the excipients in KEMOPREV IV listed in 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 subacute 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 QT_c interval. A specific thorough QT/QT_c study was conducted in healthy volunteers for definitive data demonstrating the effect of palonosetron on QT/QT_c (see section 5.1).

However, as for other 5-HT_3-antagonists, caution should be exercised in the use of KEMOPREV IV 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, brady dysrhythmias, conduction disturbances and inpatients taking anti-dysrhythmias medicines or other medicine 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 medicine (including selective serotonin reuptake inhibitors (SSRIs) and serotonin noradrenaline reuptake inhibitors (SNRIs). Appropriate observation of patients for serotonin syndrome-like symptoms is advised.

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

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 isoenzyme at clinically relevant concentrations.

Chemotherapeutic medicines

In preclinical studies, palonosetron did not inhibit the antitumour 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 medicine

Palonosetron has been administered safely with analgesics, antiemetic/anti-nauseants, antispasmodics and anticholinergic medicine.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Breastfeeding

As there are no data concerning palonosetron excretion 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 palonosetron may induce dizziness, somnolence or fatigue, patients should be cautioned when driving or operating machines.

4.8 Undesirable effects

Summary of safety profile

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

Tabulated summary of adverse reactions

The table below shows all adverse drug reactions (ADRs) observed during clinical trials and postmarket spontaneous reports with palonosetron hydrochloride.

System Organ Class	**Frequency**	
	Frequent	**Less Frequent**
Immune system disorders		Hypersensitivity, anaphylaxis, anaphylactic/anaphylactoid reactions and shock
Metabolism and nutrition disorders		Hyperkalaemia, metabolic disorders, hypocalcaemia, hypokalaemia, anorexia, hyperglycaemia, appetite decreased
Psychiatric disorders		Anxiety, euphoric mood

Nervous system disorders	Headache Dizziness	Somnolence, insomnia, paraesthesia, hypersomnia, peripheral sensory neuropathy
Eye disorders		Eye irritation, amblyopia
Ear and labyrinth disorders		Motion sickness, tinnitus
Cardiac disorders		Tachycardia, bradycardia, extrasystoles, myocardial ischaemia, sinus tachycardia, sinus dysrhythmias, supraventricular extrasystoles
Vascular disorders		Hypotension, hypertension, vein discolouration, vein distended
Respiratory, thoracic and mediastinal disorders		Hiccups
Gastrointestinal disorders	Constipation Diarrhoea	Dyspepsia, abdominal pain, abdominal pain upper, dry mouth, flatulence
Hepatobiliary disorders		Hyperbilirubinaemia

Skin and subcutaneous tissue disorders		Dermatitis allergic, pruritic rash
Musculoskeletal and connective tissue disorders		Arthralgia
Renal and urinary disorders		Urinary retention, glycosuria
General disorders and administration site conditions		Asthenia, pyrexia, fatigue, feeling hot, influenza like illness Injection site reaction*
Investigations		Elevated transaminases-, electrocardiogram QT prolonged

* Includes the following: 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 professionals are asked to report any suspected adverse 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

4.9 Overdose

No case of overdose has been reported.

Doses of up to 6 mg have been used in adult clinical studies. The highest dose group showed a similar incidence of adverse reactions compared to the other dose groups and no dose response effects were observed. In the unlikely event of overdose with KEMOPREV IV, 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 KEMOPREV IV overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and Class: 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, 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 maximum Plasma concentration (C_{max}) and area under the concentration time curve (AUCO∞) are generally dose-proportional over the dose range of 0,3 - 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.

Biotransformation

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.

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.

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 haemodialysis 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid monohydrate

D-Mannitol

Edetate disodium dihydrate

Trisodium dihydrate citrate

Water for injection

6.2 Incompatibilities

This medicinal product must not be mixed with other medicine.

6.3 Shelf life

24 months.

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

6.4 Special precautions for storage

Store at or below 25 ºC. Do not refrigerate.

Protect from light. Store vial in carton until required for use.

Upon opening of the vial, any unused solution should be discarded.

6.5 Nature and contents of container

KEMOPREV IV is presented in type I transparent glass vial with 8 mL capacity with a chlorobutyl siliconised fluorotec rubber stopper and aluminium cap with polypropylene top, with self-adhesive identification label, packed into a cardboard carton and a leaflet.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Austell Pharmaceuticals (Pty) Ltd

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2193

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8. REGISTRATION NUMBER

53/5.10/0647

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21 February 2023

10. DATE OF REVISION OF THE TEXT