APPROVED PROFESSIONAL INFORMATION

S4

1. NAME OF THE MEDICINAL PRODUCT:

PALONOSETRON 0,25 TEVA (solution for injection)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each ml of solution contains 0,05 mg palonosetron (as hydrochloride).

Each vial of 5 ml of solution contains 0,25 mg palonosetron (as hydrochloride).

Excipients with known effect:

Each vial contains less than 1 mmol sodium (23 mg) (see **section 4.4**).

For the full list of excipients, see **section 6.1.**

3. PHARMACEUTICAL FORM:

Sterile, clear solution in a 10 ml single use glass vial.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications:

PALONOSETRON 0,25 TEVA is indicated for the prevention of acute nausea and vomiting associated with moderately or highly emetogenic cancer chemotherapy.

4.2 Posology and method of administration:

Use in adults:

0,25 mg PALONOSETRON 0,25 TEVA administered as a single intravenous bolus approximately 30 minutes before the start of chemotherapy. PALONOSETRON 0,25 TEVA should be injected over 30 seconds.

Repeated dosing of PALONOSETRON 0,25 TEVA within a seven day interval is not recommended.

The efficacy of PALONOSETRON 0,25 TEVA 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:

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.

Paediatric population:

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

Method of administration:

For intravenous use.

4.3 Contraindications:

Hypersensitivity to the active substance, palonosetron or to any of the excipients of PALONOSETRON 0,25 TEVA listed in **section 6.1.**

4.4 Special warnings and precautions for use:

As PALONOSETRON 0,25 TEVA 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 0,75 mg palonosetron.

At all dose levels tested, PALONOSETRON 0,25 TEVA did not induce clinically relevant prolongation of the QTc interval. A specific thorough QT/QTc study was conducted in healthy volunteers for definitive data demonstrating the effect of PALONOSETRON 0,25 TEVA on QT/QTc.

However, as for other 5-HT_3 antagonists, caution should be exercised in the use of PALONOSETRON 0,25 TEVA 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, bradydysrhythmias, and conduction disturbances and in patients taking anti-dysrhythmic medicines or other medicinal products 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 medication including selective serotonin reuptake inhibitors (SSRI) and serotonin noradrenaline reuptake inhibitors (SNRis). Appropriate observation of patients for serotonin syndrome like symptoms is advised.

PALONOSETRON 0,25 TEVA should not be used to prevent or treat nausea and vomiting in the days following chemotherapy if not associated with another chemotherapy administration.

PALONOSETRON 0,25 TEVA contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially ‘sodium-free’.

Cases of myocardial ischemia have been reported in patients treated with palonosetron. In some patients, especially in the case of intravenous administration, symptoms appeared immediately after administration of palonosetron. Patients should be alerted to the signs and symptoms of myocardial ischaemia.

4.5 Interaction with other medicinal products and other forms of interaction:

PALONOSETRON 0,25 TEVA is mainly metabolised by CYP2D6, with minor contribution by CYP3M and CYP1A2 isoenzymes. Based on *in vitro* studies, PALONOSETRON 0,25 TEVA does not inhibit or induce cytochrome P450 isoenzyme at clinically relevant concentrations.

Chemotherapeutic medicines:

In preclinical studies, PALONOSETRON 0,25 TEVA 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 0,25 TEVA 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 0,25 TEVA 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 0,25 TEVA has been administered safely with corticosteroids.

Serotonergic Medication.(eg. SSRis and SNRis):

There have been reports of serotonin syndrome following concomitant use of 5-HT_3 antagonists and other serotonergic medication (including SSRis and SNRis).

Other medicinal products:

PALONOSETRON 0,25 TEVA has been administered safely with analgesics, antiemetic/antinauseants, antispasmodics and anticholinergic medicinal products.

4.6 Fertility, pregnancy and lactation:

Pregnancy:

For PALONOSETRON 0,25 TEVA no clinical data on exposed pregnancies are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. Only limited data from animal studies are available regarding the placental transfer.

There is no experience of PALONOSETRON 0,25 TEVA in human pregnancy. Therefore, PALONOSETRON 0,25 TEVA should not be used in pregnant women.

Breastfeeding:

As there are no data concerning PALONOSETRON 0,25 TEVA excretion in breast milk, breastfeeding should be discontinued during therapy.

Fertility:

There are no data concerning the effect of PALONOSETRON 0,25 TEVA 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 0,25 TEVA may induce dizziness, somnolence or fatigue, patients should be cautioned when driving or operating machines.

4.8 Undesirable effects:

In studies in adults at a dose of 0,25 mg the most frequently observed adverse reactions, at least possibly related to palonosetron, were headache and constipation.

In the studies the following adverse reactions (ARs) were observed as possibly or probably related to palonosetron.

Within each frequency grouping, adverse reactions are presented below in order of decreasing seriousness.

Immune system disorders:

Frequency unknown: Hypersensitivity, anaphylaxis, anaphylactic/anaphylactoid reactions and shock.

Metabolism and nutrition disorders:

Less frequent: Hyperkalaemia, metabolic disorders, hypocalcaemia, hypokalaemia, anorexia, hyperglycaemia, appetite decreased.

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, sinus tachycardia, sinus dysrhythmia, supraventricular extrasystoles.

Frequency unknown: myocardial ischemia (see **section 4.4**)

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, abdominal pain upper, dry mouth, flatulence.

Hepatobiliary disorders:

Less frequent: Hyperbillirubinaemia.

Skin and subcutaneous tissue disorders:

Less frequent: Dermatitis allergic, pruritic rash.

Musculoskeletal and connective tissue disorders:

Less frequent: Arthralgia.

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, injection site reaction (Includes the following: 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 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 adult 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 PALONOSETRON 0,25 TEVA, 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 PALONOSETRON 0,25 TEVA overdose. ·

5. Pharmacological properties:

5.1 Pharmacodynamic properties:

Pharmacological classification: A. 5.10 Serotonin antagonists.

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

ATC code: A04AA05.

Mode of Action:

Palonosetron is a potent and selective serotonin subtype 3 (5-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-HT_1, 5-HT_2 and 5-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 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.

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-HT3 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:

Mannitol

Edetate Disodium

Sodium Citrate Dehydrate,

Citric Acid Monohydrate

Hydrochloric Acid solution 10 % w/w

Sodium Hydroxide solution 10 % w/w

Water for injection

6.2 Incompatibilities:

Not applicable.

6.3 Shelf life:

24 months.

6.4 Special precautions for storage:

Store between 20 ºC and 25 ºC.

Protect from freezing.

Protect from light.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container:

PALONOSETRON 0,25 TEVA is a sterile clear colourless solution and is supplied in a pack of one 10 ml single use Type I glass vial with a grey chlorobutyl rubber stopper and blue aluminium cap, which contains 5 ml of the solution individually packaged in a carton.

Each vial contains one dose.

Available in packs of one 10 ml vial containing 5 ml of solution.

6.6 Special precautions for disposal and other handling:

Instructions for use and handling:

Single use only, any unused solution should be discarded.

7. MARKETING AUTHORISATION HOLDER:

Teva Pharmaceuticals (Pty) Ltd.

Maxwell Office Park

Magwa Crescent West

Waterfall City

Midrand

Gauteng

2090

8. MARKETING AUTHORISATION NUMBER(S):

49/5.10/1130

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION:

05 July 2022

10. DATE OF REVISION OF THE TEXT

23 February 2023