PROFESSIONAL INFORMATION

PALTON

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

PALTON 250 micrograms solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml vial contains palonosetron hydrochloride equivalent to palonosetron 250 micrograms (palonosetron 50 micrograms/1 ml).

Excipient with known effect:

Each vial contains less than 1 mmol sodium (23 mg) per vial.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

PALTON is a clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PALTON is indicated for the prevention of:

- acute nausea and vomiting associated with highly emetogenic cancer chemotherapy and;
- nausea and vomiting associated with moderately emetogenic cancer chemotherapy.

4.2 Posology and method of administration

Posology

250 micrograms palonosetron (1 PALTON vial) administered as a single intravenous bolus approximately 30 minutes before the start of chemotherapy. PALTON should be injected over 30 seconds.

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

The efficacy of PALTON 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 required in elderly patients.

Use in patients with renal impairment

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

Paediatric population

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

Method of administration

For intravenous use.

Administered as a single intravenous bolus over 30 seconds and administered approximately 30 minutes before the start of chemotherapy.

4.3 Contraindications

Hypersensitivity to the active substance, palonosetron, or to any of the excipients of PALTON listed in section 6.1.

4.4 Special warnings and precautions for use

Palonosetron may increase large bowel transit time; hence, 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 tested dose levels, palonosetron did not induce clinically relevant QTc interval prolongation. However, as for other 5-HT_3 antagonists, caution should be exercised in the concomitant use of PALTON 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, brady-dysrhythmias, conduction disturbances and in patients taking anti-dysrhythmic medicines or other medicines that lead to electrolyte abnormalities. Hypokalemia 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 for serotonin syndrome-like symptoms is recommended.

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

PALTON 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:

Results from preclinical studies indicate that palonosetron does not inhibit the anti-tumour activity of the five chemotherapeutic medicines tested (i.e. cisplatin, cyclophosphamide, cytarabine, doxorubicin and mitomycin C).

Metoclopramide:

Results from a clinical study indicate no significant pharmacokinetic interaction 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 concurrent 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

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.

PALTON should not be used in pregnant women as there is no experience of palonosetron in human pregnancy.

Breastfeeding

Breastfeeding should be discontinued during therapy since there is no data concerning excretion of palonosetron in breast milk.

Fertility

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

4.7 Effects on ability to drive and use machines

There is no data available of the effects on the ability to drive and use machines. However, since PALTON may induce dizziness, somnolence or fatigue, patients should be cautioned when driving or operating machines.

4.8 Undesirable effects

Summary of the safety profile

The most frequent adverse reactions observed during clinical studies that were at least possibly related to palonosetron, were headache and constipation.

Tabulated list of adverse reactions

Immune system disorders:

Less frequent: Hypersensitivity reactions, anaphylaxis, anaphylactic/ anaphylactoid reactions and shock.

Metabolism and nutrition:

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

Psychiatric disorders:

Less frequent: Anxiety and euphoric mood.

Nervous system disorders:

Frequent: Headache and dizziness.

Less frequent: Somnolence, insomnia, paraesthesia, hypersomnia and peripheral sensory neuropathy.

Eye disorders:

Less frequent: Eye irritation and amblyopia.

Ear and labyrinth disorders:

Less frequent: Motion sickness and tinnitus.

Cardiac disorders:

Less frequent: Tachycardia, bradycardia, extrasystoles, myocardial ischaemia, sinus tachycardia, sinus dysrhythmia, supraventricular extrasystoles.

Vascular disorders:

Less frequent: Hypotension, hypertension, vein discolouration and vein distention.

Respiratory, thoracic and mediastinal disorders:

Less frequent: Hiccups.

Gastrointestinal disorders:

Frequent: Constipation and diarrhoea.

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

Hepato-biliary disorders:

Less frequent: Hyperbilirubinaemia.

Skin and subcutaneous tissue disorders:

Less frequent: Allergic dermatitis and pruritic rash.

Musculoskeletal, connective tissue and bone disorders:

Less frequent: Arthralgia.

Renal and urinary disorders:

Less frequent: Urinary retention and glycosuria.

General disorders and administrative site conditions:

Less frequent: Asthenia, pyrexia, fatigue, feeling hot, influenza like illness and injection site reactions (burning, induration, discomfort and pain).

Investigations

Less frequent: Elevated transaminases and 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 Reaction Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

No cases of overdose have 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, it 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 overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A. 5.10 Serotonin antagonists.

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

ATC code: A04AA05.

Mechanism of action

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 ($AUC_{0-\infty}$) are generally dose-proportional over the dose range of 0,3 – 90 µg/kg in healthy subjects and in cancer patients.

Pharmacokinetic simulations indicate that the overall exposure ($AUC_{0-\infty}$) of 250 micrograms intravenous palonosetron administered once daily for 3 consecutive days was similar to a single intravenous dose of 750 micrograms, although C_{max} of the 750 micrograms single dose was higher.

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: approximately 40 % is eliminated through the kidneys and 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. Clinical pharmacokinetic parameters however 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 in the urine within 144 hours 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:

The pharmacokinetic profile of palonosetron is not affected by age. No dosage adjustment is necessary in elderly patients.

Gender:

The pharmacokinetic profile of palonosetron is not affected by gender. No dosage adjustment is necessary based on gender.

Paediatric patients:

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

Renal Impairment:

Mild to moderate renal impairment does not significantly affect the pharmacokinetic parameters of palonosetron. Severe renal impairment reduces renal clearance; however, total body clearance in these patients is similar to healthy subjects. Hence, no dosage adjustment is necessary in patients with renal insufficiency. No pharmacokinetic data in haemodialysis patients is available.

Hepatic Impairment:

Hepatic impairment does not significantly affect total body clearance of palonosetron compared to healthy subjects. Even though 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

Disodium edetate

Hydrochloric acid, concentrated (for pH adjustment)

Mannitol

Sodium citrate

Sodium hydroxide (for pH adjustment)

Water for injection

6.2 Incompatibilities

PALTON must not be mixed with other medicines.

6.3 Shelf life

5 years.

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

6.4 Special precautions for storage

Store at or below 25 °C.

Store in original packaging to protect from light.

6.5 Nature and contents of container

PALTON is packed in 5 ml clear, transparent, type I glass vials with grey chlorobutyl, type I rubber stoppers and aluminum seals with polypropylene red coloured flip-off buttons. The vials are packed in outer cartons.

6.6 Special precautions for disposal and other handling of the product

Single use only. Any unused solution should be discarded.

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Activo Health (Pty) Ltd

Block B, Arena Office Park

272 West Avenue

Centurion

0157

8. REGISTRATION NUMBER(S)

To be allocated.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

To be allocated.

10. DATE OF REVISION OF THE TEXT