

UNIPAL

Palonosetron Hydrochloride 250 micrograms Solution for Injection (5 ml)

COMPOSITION:

Each mL contains:

Palonosetron Hydrochloride equivalent to Palonosetron0.05mg

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

PRODUCT DESCRIPTION

Solution for injection

Clear, colourless solution

PHARMACODYNAMICS

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

Palonosetron is a selective high-affinity receptor antagonist of the 5HT₃ receptor.

The effect of palonosetron on blood pressure, heart rate, and ECG parameters including QTc was found comparable to ondansetron and dolasetron.

Paediatric population

Prevention of Chemotherapy Induced Nausea and Vomiting (CINV):

Reported efficacy of Palonosetron i. v at single dose of 10 µg/kg compared to 3µg/kg is 54.1 % and 37.1 % respectively. No safety concerns are available at either dose level.

It is also reported that paediatric patients require a higher palonosetron dose than adults to prevent chemotherapy-induced nausea and vomiting, the safety profile is consistent with the established profile in adults.

Prevention of Post Operative Nausea and Vomiting (PONV):

The proportion of patients without emesis during 0-72 hours post operatively was similar after palonosetron 1 µg/kg or 3 µg/kg (88% vs 84%).

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 0.3-90 µg/kg.

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, which have less than 1 % of the 5HT₃ receptor antagonist activity of palonosetron. 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 [¹⁴C]-palonosetron, approximately 80 % of the dose is recovered within 144 hours in the urine with palonosetron representing approximately 40 % of the administered dose, as unchanged active substance. The low total body clearance and large volume of distribution results in a terminal elimination half-life in plasma of approximately 40 hours.

Pharmacokinetics in special populations

Elderly people

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 population

When the dose was increased from 10 µg/kg to 20 µg/kg a dose-proportional increase in mean AUC was observed. Following single dose intravenous infusion of palonosetron 20 µg/kg, peak plasma concentrations (C_T) reported at the end of the 15 minute infusion were highly variable in all age groups and tended to be lower in patients < 6 years than in older paediatric patients. Median half-life was 29.5 hours in overall age groups and ranged from about 20 to 30 hours across age groups after administration of 20 µg/kg.

The total body clearance (L/h/kg) in patients 12 to 17 years old was similar to that in healthy adults. There are no apparent differences in volume of distribution when expressed as L/kg.

Renal impairment

Mild to moderate renal impairment does not significantly affect palonosetron pharmacokinetic parameters. Severe renal impairment reduces renal clearance, however total body clearance is similar. 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. While the terminal elimination half-life and mean systemic exposure of palonosetron is increased with severe hepatic impairment, this does not warrant dose reduction.

INDICATION

UNIPAL Palonosetron Hydrochloride 250 micrograms solution for injection is indicated for

Chemotherapy-Induced Nausea and Vomiting

Adults and Paediatric Patients 1 month of Age and Older

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

Postoperative Nausea and Vomiting

- Prevention of postoperative nausea and vomiting (PONV) for up to 24 hours following surgery. Efficacy beyond 24 hours has not been demonstrated.

As with other antiemetics, routine prophylaxis is not recommended in patients in whom there is little expectation that nausea and/or vomiting will occur postoperatively. In patients where nausea and vomiting must be avoided during the postoperative period, UNIPAL Palonosetron Hydrochloride 250 micrograms solution for injection is recommended even where the incidence of postoperative nausea and/or vomiting is low.

RECOMMENDED DOSE

This medicinal product should be administered by a healthcare professional under appropriate medical supervision.

Posology

Adults

Chemotherapy-Induced Nausea and Vomiting

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

The efficacy of **UNIPAL** 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.

Postoperative Nausea and Vomiting

75 micrograms palonosetron administered as a single intravenous bolus over 10 seconds immediately before the induction of anaesthesia

Paediatric population

Chemotherapy-Induced Nausea and Vomiting

Children and Adolescents (aged 1 month to 17 years):

20 micrograms/kg (the maximum total dose should not exceed 1500mcg) palonosetron administration as a single 15 minutes intravenous infusion beginning approximately 30 minutes before the start of chemotherapy.

The safety and efficacy of **UNIPAL** in children aged less than 1 month have not been established. No data are available.

Postoperative Nausea and Vomiting

Safety and effectiveness in patients below the age of 18 years have not been established.

Elderly population

No dose adjustment is necessary for the elderly.

Hepatic impairment

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

Renal impairment

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

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

ROUTE OF ADMINISTRATION

To be administered intravenously

CONTRAINDICATION

Hypersensitivity to the active substance or to any of the excipients

WARNING AND PRECAUTIONS

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.

Reports indicate that at all dose levels tested, palonosetron did not induce clinically relevant prolongation of the QTc interval. However, as for other 5-HT₃ antagonists, caution should be exercised in the use of palonosetron 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, bradyarrhythmias, conduction disturbances and in patients taking anti-arrhythmic agents or other medicinal products that lead to QT prolongation or electrolyte abnormalities. Hypokalemia and hypomagnesaemia should be corrected prior to 5-HT₃-antagonist administration.

There have been reports of serotonin syndrome with the use of 5-HT₃ antagonists either alone or in combination with other serotonergic drugs (including selective serotonin reuptake inhibitors (SSRI) and serotonin noradrenaline reuptake inhibitors (SNRIs)). Appropriate observation of patients for serotonin syndrome-like symptoms is advised.

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

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

INTERACTIONS WITH OTHER MEDICAMENTS

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

Chemotherapeutic agents

Palonosetron did not inhibit the antitumour activity of the five chemotherapeutic agents tested (cisplatin, cyclophosphamide, cytarabine, doxorubicin and mitomycin C).

Metoclopramide

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

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 reported to be administered safely with corticosteroids.

Serotonergic Drugs (e.g. SSRIs and SNRIs)

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

Other medicinal products

Palonosetron has been reported to be administered safely with analgesics, antiemetic/ antinauseants, antispasmodics and anticholinergic medicinal products.

PREGNANCY AND LACTATION

Pregnancy

There is no experience of palonosetron in human pregnancy. Therefore, palonosetron should not be used in pregnant women unless it is considered essential by the physician.

Breast-feeding

As there are no data concerning palonosetron excretion in breast milk, breast-feeding should be discontinued during therapy.

Fertility

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

SIDE EFFECTS

Adverse reactions which have been reported with Palonosetron include:

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 arrhythmia, supraventricular extrasystoles

Vascular disorders: Hypotension, hypertension, vein discoloration, vein distended

Respiratory, thoracic and mediastinal disorders: Hiccups

Gastrointestinal disorders: Constipation, Diarrhoea, Dyspepsia, abdominal pain, 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 which includes burning, induration, discomfort and pain

Investigations: Elevated transaminase level, electrocardiogram QT prolonged

Paediatric population

The following adverse reactions were reported for palonosetron in paediatric population receiving palonosetron for up to 4 chemotherapy cycles.

Nervous system disorders: Headache, Dizziness, dyskinesia

Cardiac disorders: Electrocardiogram QT prolonged conduction disorder, sinus tachycardia

Respiratory, thoracic and mediastinal disorders: Cough, dyspnoea, epistaxis

Skin and subcutaneous tissue disorders: Dermatitis allergic, pruritus, skin disorder, urticaria

General disorders and administration site conditions: Pyrexia, infusion site pain, infusion site reaction, pain.

SYMPTOMS AND TREATMENT OF OVERDOSE

No case of overdose has been reported.

Paediatric population

No case of overdose has been reported in paediatric population.

EFFECT ON ABILITY TO DRIVE AND USE MACHINE

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.

INSTRUCTION FOR USE

Single use only, any unused solution should be discarded.

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

Incompatibilities

This medicinal product must not be mixed with other medicinal products.

Pharmaceutical particulars

List of excipients

Mannitol

Disodium edetate

Sodium citrate

Citric acid monohydrate

Sodium hydroxide (for pH adjustment)

Hydrochloric acid (for pH adjustment)

Water for injections

Nature and contents of container

LYO Imp (Tubular) glass Vial with bromobutyl siliconized rubber stopper and plastic cap with Aluminium Seal. Available in packs of 1 vial containing 5ml of solution.

STORAGE CONDITION

Store below 30°C, protect from light.

SHELF LIFE

24 months

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

THERAPEUTICS CODE

ATC code : A04AA05.

PRESENTATIONS

UNIPAL Palonosetron Hydrochloride 250 micrograms solution for Injection is supplied as 5ml clear colourless solution vial.

MANUFACTURED BY:

USV Private Limited

H-13, 16, 16A, 17, 18, 19, 20, 21, E-22,
OIDC, Mahatma Gandhi Udyog Nagar,
Dabhel, Daman – 396210, India.

PRODUCT REGISTRATION HOLDER:

UNIMED SDN BHD

No. 53, Jalan Tembaga SD 5/2B, Bandar Sri
Damansara,
52200 Kuala Lumpur, Malaysia.

DATE OF REVISION

02.11.2022

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