For the use of an Oncologist or a Hospital or a Laboratory only 8027958-9093

CHEPATRON

(Palonosetron Hydrochloride Injection)

COMPOSITION

Each 5 ml contains :

Palonosetron Hydrochloride equivalent to

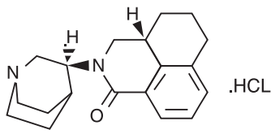
Palonosetron 0.25 mg

Water for Injections I.P. q.s.

DESCRIPTION

Chepatron (Palonosetron hydrochloride) is an antiemetic and antinauseant agent. It is a selective serotonin subtype 3 (5-HT_3) receptor antagonist with a strong binding affinity for this receptor. Chemically, palonosetron hydrochloride is : (3aS)-2-[(S)-1-Azabicyclo[2.2.2]oct-3-yl]-2,3,3a,4,5,6-hexahydro-1-oxo-1Hbenz[de]isoquinoline hydrochloride.

The empirical formula is $C_{19}H_{24}N_2O$.HCl, with a molecular weight of 332.87. Palonosetron hydrochloride exists as a single isomer and has the following structural formula :



.HCL

Palonosetron hydrochloride is a white to off-white crystalline powder. It is freely soluble in water, soluble in propylene glycol, and slightly soluble in ethanol and 2-propanol.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Palonosetron is a selective 5-HT_3 receptor antagonist with a strong binding affinity for this receptor and little or no affinity for other receptors. The effect of palonosetron on blood pressure, heart rate, and ECG parameters including QTc were comparable to ondansetron and dolasetron in clinical trials. In non-clinical studies palonosetron possesses the ability to block ion channels involved in ventricular de- and re-polarization and to prolong action potential duration. In clinical trials, the dose-response relationship to the QTc interval has not been fully evaluated.

Pharmacokinetics

Palonosetron has a volume of distribution of around 7 to 8 litres/kg; plasma protein binding is about 62%. About 50% of a dose is metabolised in the liver by cytochrome P450 isoenzymes (notably CYP2D6, but also CYP3A4 and CYP1A2). About 80% of a dose is recovered in the urine within 144 hours, as palonosetron and its metabolites. The mean elimination half-life is reported to be about 40 hours.

INDICATIONS

Palonosetron is indicated for:

For prevention of nausea/vomiting associated with initial and repeat course of moderately and highly emetogenic cancer chemotherapy

CONTRAINDICATIONS

The Product is contraindicated in the following situations : patients previously sensitive to the drugs components or to any of the excipients of the product.

WARNINGS AND PRECAUTIONS

General

Hypersensitivity reactions may occur in patients who have exhibited hypersensitivity to other selective 5-HT_3 receptor antagonists. Although palonosetron has been safely administered to 192 patients with pre-existing cardiac impairment in the Phase 3 studies, palonosetron should be administered with caution in patients who have or may develop prolongation of cardiac conduction intervals, particularly QTc.

These include patients with hypokalemia or hypomagnesemia, patients taking diuretics with potential for inducing electrolyte abnormalities, patients with conge nital QT syndrome, patients taking anti-arrhythmic drugs or other drugs which lead to QT prolongation, and cumulative high dose anthracycline therapy. In 3 pivotal trials, ECGs were obtained at baseline and 24 hours after subjects received palonosetron or a comparator drug. In a subset of patients ECGs were also obtained 15 minutes following dosing.

The percentage of patients (<1%) with changes in QT and QTc intervals (either absolute values of > 500 msec or changes of > 60 msec from baseline) was similar to that seen with the comparator drugs.

Usage in pregnancy and lactation

Pregnancy

There is no information on the use of palonosetron during pregnancy. Therefore, Palonosetron should not be used in pregnant woman, unless it is considered essential by the physician.

Lactation

There is no information on the secretion of Palonosetron in breast milk. So Palonosetron should not be given during lactation.

Usage in paediatrics

Safety & Efficacy not established in children

Usage in geriatrics

No dose adjustments or special monitoring are required for geriatric patients.

Drug interactions

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 agents

In preclinical studies, palonosetron did not inhibit the antitumour activity of the five chemotherapeutic agents 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

Chepatron has been administered safely with corticosteroids.

Other medicinal products

Chepatron has been administered safely with analgesics, antiemetic/antinauseants, antispasmodics and anticholinergic medicinal products.

ADVERSE EFFECTS

In clinical studies reported that at a dose of 250 micrograms (total 633 patients) the most frequently observed adverse reactions, at least possibly related to Palonosetron, were headache (9 %) and constipation (5 %). In the clinical studies the following adverse reactions (ARs) were reported as possibly or probably related to Palonosetron. These were classified as common (≥ 1/100 to <1/10) or uncommon (≥ 1/1,000 to < 1/100).Very rare (< 1/10,000) adverse reactions were reported post-marketing. Within each frequency grouping, adverse reactions are presented below in order of decreasing seriousness.

System organ class	Common ARs (≥ 1/100 to < 1/10)	Uncommon ARs (≥ 1/1,000 to < 1/100)	Very rare ARs° (< 1/10,000)
Immune system disorders			Hypersensitivity
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 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	

° From post-marketing experience

* Includes the following: burning, induration, discomfort and pain

DOSAGE AND ADMINISTRATION

Chemotherapy Induced Nausea and Vomiting

Dosage for Adults - a single 0.25 mg I.V. dose administered over 30 seconds. Dosing should occur approximately 30 minutes before the start of chemotherapy.

Postoperative Nausea and Vomiting

Dosage for Adults - a single 0.075 mg I.V. dose administered over 10 seconds immediately before induction of anesthesia.

Discard any unused solution after opening.

Instructions for I.V. Administration

Chepatron is supplied ready for intravenous injection. Chepatron should not be mixed with other drugs. Flush the infusion line with normal saline before and after administration of Chepatron.

Parenteral drug products should be inspected visually for particulate matter before administration, whenever solution and container permit.

OVERDOSAGE

No case of overdose has been reported.

Doses of up to 6 mg have been used in 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 Palonosetron, 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 overdose.

A single intravenous dose of palonosetron at 30 mg/kg (947 and 474 times the human dose for rats and mice, respectively, based on body surface area) was lethal to rats and mice. The major signs of toxicity were convulsions, gasping, pallor, cyanosis and collapse.

STORAGE

Store below 25°C. Protect from light. Do not freeze.

Keep out of reach of children.

EXPIRY DATE

Do not use later than the date of expiry.

PRESENTATION

Chepatron is available as 0.25 mg (free base) in 5 ml, is supplied as a single-use sterile solution in glass vial, I.V. USE ONLY.

torrent

Marketed by :
TORRENT PHARMACEUTICALS LTD.
Indrad-382 721, Dist. Mehsana, INDIA.

Manufactured by :
THEMIS MEDICARE LIMITED
Sector 6A, Plot No. 16, 17 & 18, IIE
BHEL, Haridwar - 249 403, Uttarakhand.

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