Package Insert

PALSET (Palonosetron Hydrochloride Solution for Injection 0.05 mg/ml, 5 ml vial)

Name and strength of active ingredient

Palonosetron Hydrochloride equivalent to Palonosetron 0.05 mg/ml

Product Description

A clear, colourless solution, filled in a glass container. When examined under suitable conditions of visibility it should be practically free from foreign particles.

pH: Between 3.0 to 3.9

Pharmacological properties

Pharmacodynamic properties

Pharmacotherapeutic group: Antiemetics and antinauseants, serotonin ($5HT_3$) antagonists. ATC code: A04AA05

Palonosetron is a selective high-affinity receptor antagonist of the $5HT_3$ receptor.

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 in healthy subjects and in cancer patients.
Pharmacokinetic simulations indicate that the overall exposure ($AUC_{0-\infty}$) of 0.25 mg intravenous palonosetron administered once daily for 3 consecutive days was similar to a single intravenous dose of 0.75 mg, although C_{max} of the 0.75 mg 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, about 40 % eliminated through the kidney and with approximately 50 % metabolised to form two primary metabolites, which have less than 1 % of the $5HT_3$ 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 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
The total body clearance (L/h/kg) in patients 12 to 17 years old is similar to that in healthy adults. There are no apparent differences in volume of distribution when expressed as L/kg.
Single-dose i.v. Palonosetron pharmacokinetic data was obtained from a subset of paediatric cancer patients that received 10 µg/kg or 20 µg/kg. When the dose was increased from 10µg/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 (CT) 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.

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 the 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.

Indication/Usage

Palset 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.

Posology and method of administration

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

Adults

Chemotherapy-Induced Nausea and Vomiting
250 micrograms Palonosetron administered as a single intravenous bolus approximately 30 minutes before the start of chemotherapy. Palonosetron Hydrochloride Injection should be injected over 30 seconds.

The efficacy of Palonosetron Hydrochloride Injection 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.

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 Palonosetron Hydrochloride Injection in children aged less than 1 month have not been established. No data are available.

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.

Method of administration

For intravenous use.

Contraindication

Hypersensitivity to the active substance or to any of the excipients

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 QTc interval. A specific thorough QT/QTc study was conducted in healthy volunteers for definitive data demonstrating the effect of palonosetron on QT/QTc.
However, as for other 5-HT_3 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 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 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 Hydrochloride Injection 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'.

Interaction with other medicinal products 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 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

Palonosetron has been administered safely with corticosteroids.

Serotonergic Drugs (e.g. SSRIs and SNRIs)

There have been reports of serotonin syndrome following concomitant use of 5-HT_3 antagonists and other serotonergic drugs (including SSRIs and SNRIs).

Other medicinal products

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

Fertility, pregnancy and lactation

Pregnancy

For Palonosetron 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 is available regarding the placental transfer in animal

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.

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.

Undesirable effects

The following adverse reactions (ARs) were observed as possibly or probably related to Palonosetron Hydrochloride Injection. These were classified as common or uncommon or very rare.

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

System organ class	**Common ARs**	**Uncommon ARs**	**Very rare ARs°**
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 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

Paediatric population

The following common or uncommon adverse reactions were reported for palonosetron

System organ class	**Common ARs**	**Uncommon ARs**
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

Adverse reactions were evaluated in paediatric patients receiving palonosetron for up to 4 chemotherapy cycles.

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 Palonosetron Hydrochloride Injection, 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 Hydrochloride Injection overdose.

Paediatric population
No case of overdose has been reported in paediatric clinical studies.

Ingredients

Active ingredient
Palonosetron Hydrochloride
equivalent to Palonosetron 0.05 mg/ml

Inactive ingredient
Mannitol
Citric acid monohydrate
Sodium citrate
Disodium EDTA
Sodium hydroxide
Hydrochloric acid concentrate
Water for Injection

Shelf life
36 months
Upon opening of the vial, use immediately and discard any unused solution

Storage Conditions

Store below 30°C, Protect from light.

Incompatibilities

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

Instructions for Use

Method of administration: For intravenous 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.

Dosage forms and packaging available
USP type I clear tubular blow back glass vial
Available in packs of 1 vial containing 5 ml of solution**.**

Name and address of manufacturer
INTAS PHARMACEUTICALS LTD.
Plot No.: 457 - 458, Village - Matoda, Bavla Road,
And Plot No. 191/218P, Village: Chacharwadi
Ta: Sanand, Dist. – Ahmedabad, Gujarat, INDIA.

Date of revision of PI

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