PRESCRIBING INFORMATION

(For the use of a Registered Medical Practitioner or Hospital or Laboratory only)

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

COMPOSITION:
Each ml contains:
Palonosetron Hydrochloride
equivalent to
Palonosetron 0.05 mg
Water for Injection USP Q.S.

DESCRIPTION:
Palonosetron hydrochloride is an anti-emetic and anti-nauseant agent. It is a 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,4,5,6hexahydro-1-oxo-1Hbenz [de]isoquinoline hydrochloride. The empirical formula is C19H24N2O.HCl, with a molecular weight of 332.87.

PHARMACOLOGY:

Mechanism of Action
Palonosetron is a 5-HT_3 receptor antagonist with a strong binding affinity for this receptor and little or no affinity for other receptors. 5-HT_3 receptors are found in the gut and in areas of the central nervous system associated with the regulation of nausea and vomiting, being abundant in the chemoreceptor trigger zone of the area postrema which has projections to the vomiting center located in the lateral reticular formation of the medulla oblongata. Stimulation of these receptors initiates the vomiting reflex. Peripheral 5-HT_3 receptors are located in vagal nerve terminals, which are linked to the vomiting center via the nucleus tractus solitarius. Competitive antagonism with 5-HT_3 receptor antagonists at these sites, and probably others, can block initiation of the vomiting reflex caused by emetogenic stimuli.

Pharmacokinetics Absorption:
After intravenous dosing of palonosetron in healthy subjects, an initial decline in plasma concentrations is followed by a slow elimination from the body. Mean maximum plasma concentration (C_{max}) and area under the concentration-time curve (AUC_{0}-∞) are generally dose-proportional over the dose range of 0.3–90 mcg/kg in healthy subjects.

Distribution:
Palonosetron has a volume of distribution of approximately 8.3 ± 2.5 L/kg. Approximately 62% of palonosetron is bound to plasma proteins.

Metabolism:
Palonosetron is eliminated by multiple routes with approximately 50% metabolized to form two primary metabolites: N-oxide-palonosetron and 6-S-hydroxy-palonosetron. These metabolites each have less than 1% of the 5-HT_3 receptor antagonist activity of palonosetron. In vitro metabolism studies have suggested that CYP2D6 and to a lesser extent, CYP3A4 and CYP1A2 are involved in the metabolism of palonosetron. However, clinical pharmacokinetic parameters are not significantly different between poor and extensive metabolizers of CYP2D6 substrates.

Elimination:
In healthy subjects, the total body clearance of palonosetron is 160 ± 35 mL/h/kg and renal clearance is 66.5± 18.2 mL/h/kg. Mean terminal elimination half-life was approximately 40 hours.

INDICATIONS:
Palonosetron Hydrochloride is indicated for: Moderately emetogenic cancer chemotherapy - prevention of acute and delayed nausea and vomiting associated with initial and repeat courses.

Highly emetogenic cancer chemotherapy - prevention of acute nausea and vomiting associated with initial and repeat courses. Prevention of postoperative nausea and vomiting (PONV) for up to 24 hours following surgery.

DOSAGE AND ADMINISTRATION:
Chemotherapy-Induced Nausea and Vomiting:
Adult Dosage: 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
Adult Dosage: a single 0.075 mg I.V. dose administered over 10 seconds immediately before the induction of anesthesia.

CONTRAINDICATIONS:
Palonosetron Hydrochloride is contraindicated in patients known to have hypersensitivity to the drug or any of its components.

WARNINGS AND PRECAUTIONS:
Hypersensitivity
Hypersensitivity reactions may occur in patients who have exhibited hypersensitivity to other 5HT_3 receptor antagonists.

QTc Intervals
Palonosetron should be administered with caution in patients who have or may develop prolongation of cardiac conduction intervals, particularly QTc.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Treatment with palonosetron produced increased incidences of adrenal benign pheochromocytoma and combined benign and malignant pheochromocytoma, increased incidences of pancreatic Islet cell adenoma and combined adenoma and carcinoma and pituitary adenoma in male rats. In female rats, it produced hepatocellular adenoma and carcinoma and increased the incidences of thyroid C-cell adenoma and combined adenoma and carcinoma. Palonosetron was not genotoxic in the Ames test, the Chinese hamster ovarian cell (CHO/HGPRT) forward mutation test, the ex vivo hepatocyte unscheduled DNA synthesis (UDS) test or the mouse micronucleus test. It was, however, positive for clastogenic effects in the Chinese hamster ovarian (CHO) cell chromosomal aberration test.

Palonosetron at oral doses up to 60 mg/kg/day was found to have no effect on fertility and reproductive performance of male and female rats.

USE IN SPECIFIC POPULATIONS:
Pregnancy Teratogenic Effects: Category B There are no adequate and well-controlled studies in pregnant women, so Palonosetron should be used during pregnancy only if clearly needed.

Labor and Delivery Palonosetron has not been administered to patients undergoing labor and delivery, so its effects on the mother or child are unknown.

Nursing Mothers It is not known whether Palonosetron is excreted in human milk. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

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

Geriatric Use No dose adjustment or special monitoring is required for geriatric patients.

Renal Impairment Dosage adjustment is not necessary in patients with any degree of renal impairment.

Hepatic Impairment Dosage adjustment is not necessary in patients with any degree of hepatic impairment.
Race No dose adjustment is required.

DRUG INTERACTIONS:
Palonosetron is eliminated from the body through both renal excretion and metabolic pathways with the latter mediated via multiple CYP enzymes.

The potential for clinically significant drug interactions with palonosetron appears to be low.

ADVERSE EFFECTS:
Headache, constipation, chills, pyrexia, sinusitis.

OVERDOSAGE:
There is no known antidote to Palonosetron. Overdose 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. The major signs of toxicity include convulsions, labored breathing, and salivation.

PRESENTATION:
Palonosetron Hydrochloride Injection is packed in 5 ml clear glass vial.

STORAGE:
Store below 30°C, protect from light.

Manufactured by:
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INTAS PHARMACEUTICALS LTD.
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