1. Name of the medicinal product

INN Name: Palonosetron Hydrochloride Injection 0.25mg/5mL

Trade Name: PALOX

Strength: 0.25mg/5mL

Pharmaceutical form: Injection

2. Qualitative and quantitative composition

Each mL contains Palonosetron Hydrochloride equivalent to 0.25mg of Palonosetron, Mannitol USP, Edetate Disodium USP, Sodium Citrate Dihydrate (Tri Sodium Citrate Dihydrate) USP, Citric acid Monohydrate USP, Sodium Hydroxide USP-NF, Hydrochloric Acid USP-NF and Water for Injection IH.

3. Pharmaceutical form

Dosage form: Injection

Description: A clear colourless solution, in 5mL Type-I, clear tubular glass vial with 20mm grey bromo butyl rubber stopper and 20mm Violet color flip off aluminium seal.

When reconstituted as directed the solution should be clear, light to dark tan colored solution.

4. CLINICAL PHARMACOLOGY

4.1 Therapeutic indications

Chemotherapy-Induced Nausea and Vomiting in Adults 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.

Chemotherapy-Induced Nausea and Vomiting in Pediatric Patients Aged 1 month to Less than 17 Years.

Palonosetron Hydrochloride injection is indicated for prevention of acute nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including highly emetogenic cancer chemotherapy.

Postoperative Nausea and Vomiting in Adults

Palonosetron Hydrochloride injection is indicated for 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, Palonosetron Hydrochloride injection is recommended even where the incidence of postoperative nausea and/or vomiting is low.

4.2 Posology and method of administration

Recommended Dosing

Chemotherapy-Induced Nausea and Vomiting

Age	**Dose***	**Infusion Time**
Adults	**0.25 mg x 1**	Infuse over **30 seconds** beginning approx. 30 min before the start of chemo
Pediatrics (1 month to less than 17 years)	**20 micrograms per kilogram** (max 1.5 mg) x 1	Infuse over **15 minutes** beginning approx. 30 min before the start of chemo

Postoperative Nausea and Vomiting

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

Palonosetron Hydrochloride injection is supplied ready for intravenous administration at a concentration of 0.05 mg/mL (50 mcg/ mL). Palonosetron Hydrochloride injection should not be mixed with other drugs. The infusion line should be flushed with normal saline before and after administration of Palonosetron Hydrochloride injection. Parenteral drug products should be inspected visually for particulate matter and discoloration before administration, whenever solution and container permit

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Hypersensitivity

Hypersensitivity reactions, including anaphylaxis, have been reported with or without known hypersensitivity to other 5-HT_3 receptor antagonists.

Serotonin Syndrome

The development of serotonin syndrome has been reported with 5-HT_3 receptor antagonists. Most reports have been associated with concomitant use of serotonergic drugs (e.g., selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors, mirtazapine, fentanyl, lithium, tramadol, and intravenous methylene blue). Some of the reported cases were fatal. Serotonin syndrome occurring with overdose of another 5-HT_3 receptor antagonist alone has also been reported. The majority of reports of serotonin syndrome related to 5-HT_3 receptor antagonist use occurred in a post-anesthesia care unit or an infusion center.

Symptoms associated with serotonin syndrome may include the following combination of signs and symptoms: mental status changes (e.g. agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, and hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, with or without gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Patients should be monitored for the emergence of serotonin

syndrome, especially with concomitant use of Palonosetron Hydrochloride injection and other serotonergic drugs. If symptoms of serotonin syndrome occur, discontinue Palonosetron Hydrochloride injection and initiate supportive treatment. Patients should be informed of the increased risk of serotonin syndrome, especially if Palonosetron Hydrochloride injection is used concomitantly with other serotonergic drugs.

4.5 Interaction with other medicinal products and other forms of interaction

Palonosetron is eliminated from the body through both renal excretion and metabolic pathways with the latter mediated via multiple CYP enzymes. Further *in vitro* studies indicated that palonosetron is not an inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2D6, CYP2E1 and CYP3A4/5 (CYP2C19 was not investigated) nor does it induce the activity of CYP1A2, CYP2D6, or CYP3A4/5. Therefore, the potential for clinically significant drug interactions with palonosetron appears to be low.

Serotonin syndrome (including altered mental status, autonomic instability, and neuromuscular symptoms) has been described following the concomitant use of 5-HT3 receptor antagonists and other serotonergic drugs, including selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs).

Coadministration of 0.25 mg I.V. palonosetron and 20 mg I.V. dexamethasone in healthy subjects revealed no pharmacokinetic drug-interactions between palonosetron and dexamethasone.

In an interaction study in healthy subjects where palonosetron 0.25 mg (I.V. bolus) was administered on day 1 and oral aprepitant for 3 days (125 mg/80 mg/80 mg), the pharmacokinetics of palonosetron were not significantly altered (AUC: no change, C_{max}: 15% increase).

A study in healthy volunteers involving single-dose I.V. Palonosetron (0.75mg) and steady state oral metoclopramide (10 mg four times daily) demonstrated no significant pharmacokinetic interaction.

In controlled clinical trials, Palonosetron Hydrochloride injection has been safely administered with corticosteroids, analgesics, antiemetics/antinauseants, antispasmodics and anticholinergic agents.

Palonosetron did not inhibit the antitumor activity of the five chemotherapeutic agents tested (cisplatin, cyclophosphamide, cytarabine, doxorubicin and mitomycin C) in murine tumor models.

4.6 Pregnancy and lactation

Pregnancy

Pregnancy Category B

Risk Summary

Adequate and well controlled studies with Palonosetron Hydrochloride injection have not been conducted in pregnant women. In animal reproduction studies, no effects on embryo-fetal development were observed with the administration of oral palonosetron during the period of organogenesis at doses up to 1894 and 3789 times the recommended human intravenous dose in rats and rabbits, respectively. Because animal reproduction studies are not always predictive of human response, Palonosetron Hydrochloride injection should be used during pregnancy only if clearly needed.

Animal Data

In animal studies, no effects on embryo-fetal development were observed in pregnant rats given oral palonosetron at doses up to 60 mg/kg/day (1894 times the recommended human intravenous dose based on body surface area) or pregnant rabbits given oral doses up to 60 mg/kg/day (3789 times the recommended human intravenous dose based on body surface area) during the period of organogenesis.

Nursing Mothers

It is not known whether Palonosetron Hydrochloride injection is present in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants and the potential for tumorigenicity shown for palonosetron in the rat carcinogenicity study 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

Chemotherapy-Induced Nausea and Vomiting

Safety and effectiveness of Palonosetron Hydrochloride injection have been established in pediatric patients aged 1 month to less than 17 years for the prevention of acute nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including highly emetogenic cancer chemotherapy. Use is supported by a clinical trial where 165 pediatric patients aged 2 months to <17 years were randomized to receive a single dose of palonosetron 20 mcg/kg (maximum 1.5 mg) administered as an intravenous infusion 30 minutes prior to the start of emetogenic chemotherapy. While this study demonstrated that pediatric 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.

Safety and effectiveness of Palonosetron Hydrochloride injection in neonates (less than 1 month of age) have not been established.

Postoperative Nausea and Vomiting Studies

Safety and efficacy have not been established in pediatric patients for prevention of postoperative nausea and vomiting. Two pediatric trials were performed.

Pediatric Study 1, a dose finding study was conducted to compare two doses of palonosetron, 1 mcg/kg (max 0.075 mg) versus 3 mcg/kg (max 0.25 mg). A total of 150 pediatric surgical patients participated, age range 1 month to <17 years. No dose response was observed.

Pediatric Study 2, a multicenter, double-blind, double-dummy, randomized, parallel group, active control, single-dose non-inferiority study, compared I.V. palonosetron (1 mcg/kg, max 0.075 mg) versus I.V. ondansetron. A total of 670 pediatric surgical patients participated, age 30 days to <17 years. The primary efficacy endpoint, Complete Response (CR: no vomiting, no retching, and no antiemetic rescue medication) during the first 24 hours postoperatively was achieved in 78.2% of patients in the palonosetron group and 82.7% in the ondansetron group. Given the pre-specified non-inferiority margin of -10%, the stratum adjusted Mantel-Haenszel statistical non-inferiority confidence interval for the difference in the primary endpoint, complete response (CR), was [-10.5, 1.7%], therefore non-inferiority was not demonstrated. Adverse reactions to palonosetron were similar to those reported in adults.

Geriatric Use

Population pharmacokinetics analysis did not reveal any differences in palonosetron pharmacokinetics between cancer patients ≥ 65 years of age and younger patients (18 to 64

years). Of the 1374 adult cancer patients in clinical studies of palonosetron, 316 (23%) were ≥ 65 years old, while 71 (5%) were ≥ 75 years old. No overall differences in safety or effectiveness were observed between these subjects and the younger subjects, but greater sensitivity in some older individuals cannot be ruled out. No dose adjustment or special monitoring are required for geriatric patients.

Of the 1520 adult patients in Palonosetron Hydrochloride injection PONV clinical studies, 73 (5%) were ≥65 years old. No overall differences in safety were observed between older and younger subjects in these studies, though the possibility of heightened sensitivity in some older individuals cannot be excluded. No differences in efficacy were observed in geriatric patients for the CINV indication and none are expected for geriatric PONV patients. However, Palonosetron Hydrochloride injection efficacy in geriatric patients has not been adequately evaluated.

Renal Impairment

Mild to moderate renal impairment does not significantly affect palonosetron pharmacokinetic parameters. Total systemic exposure increased by approximately 28% in severe renal impairment relative to healthy subjects. Dosage adjustment is not necessary in patients with any degree of renal impairment.

Hepatic Impairment

Hepatic impairment does not significantly affect total body clearance of palonosetron compared to the healthy subjects. Dosage adjustment is not necessary in patients with any degree of hepatic impairment.

Race

Intravenous palonosetron pharmacokinetics was characterized in twenty-four healthy Japanese subjects over the dose range of 3 – 90 mcg/kg. Total body clearance was 25% higher in Japanese subjects compared to Whites, however, no dose adjustment is required. The pharmacokinetics of palonosetron in Blacks has not been adequately characterized.

4.7 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.

4.8 Undesirable effects

In clinical studies in adults at a dose of 250 micrograms (total 633 patients) the most frequently observed adverse reactions, at least possibly related to Aloxi, were headache (9 %) and constipation (5 %).

In the clinical studies the following adverse reactions (ARs) were observed as possibly or probably related to Aloxi. 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, anaphylaxis, anaphylactic/ anaphylactoid reactions and shock
Metabolism and nutrition disorders		Hyperkalaemia, metabolic disorders, hypocalcaemia, hypokalaemia, anorexia, hyperglycaemia, appetite	
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	
Vascular disorders		Hypotension, hypertension, vein discolouration, vein	
Respiratory, thoracic and mediastinal disorders		Hiccups	
Gastrointestinal disorders	Constipation Diarrhoea	Dyspepsia, abdominal pain, abdominal pain upper, dry mouth,	
Hepatobiliary disorders		Hyperbilirubinaemia	
Skin and subcutaneous tissue disorders		Dermatitis allergic, pruritic rash	
Musculoskeletal and connective tissue disorders		Arthralgia	
Renal and urinary		Urinary retention,	
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

In paediatric clinical trials for the prevention of nausea and vomiting induced by moderately or highly emetogenic chemotherapy, 402 patients received a single dose of palonosetron (3, 10 or 20 mcg/kg). The following common or uncommon adverse reactions were reported for palonosetron, none were reported at a frequency of >1%.

System organ class	Common ARs (≥1/100 to<1/10)	Uncommon ARs (≥1/1,000 to <1/100)
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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard.

4.9 Overdose

There is no known antidote to Palonosetron Hydrochloride injection. Overdose should be managed with supportive care.

Fifty adult cancer patients were administered palonosetron at a dose of 90 mcg/ kg (equivalent to 6 mg fixed dose) as part of a dose ranging study. This is approximately 25 times the recommended dose of 0.25 mg. This dose group had a similar incidence of adverse events compared to the other dose groups and no dose response effects were observed.

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.

5. Pharmacological properties

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.

Cancer chemotherapy may be associated with a high incidence of nausea and vomiting, particularly when certain agents, such as cisplatin, are used. 5-HT_3 receptors are located on the nerve terminals of the vagus in the periphery and centrally in the chemoreceptor trigger zone of the area postrema. It is thought that chemotherapeutic agents produce nausea and vomiting by releasing serotonin from the enterochromaffin cells of the small intestine and that the released serotonin then activates 5-HT_3 receptors located on vagal afferents to initiate the vomiting reflex.

Postoperative nausea and vomiting is influenced by multiple patient, surgical and anesthesia related factors and is triggered by release of 5-HT in a cascade of neuronal events involving both the central nervous system and the gastrointestinal tract. The 5-HT_3 receptor has been demonstrated to selectively participate in the emetic response.

Pharmacodynamics

The effect of palonosetron on blood pressure, heart rate, and ECG parameters including QTc were comparable to ondansetron and dolasetron in CINV clinical trials. In PONV clinical trials the effect of palonosetron on the QTc interval was no different from placebo. 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.

The effect of palonosetron on QTc interval was evaluated in a double blind, randomized, parallel, placebo and positive (moxifloxacin) controlled trial in adult men and women. The objective was to evaluate the ECG effects of I.V. administered palonosetron at single doses of 0.25, 0.75 or 2.25 mg in 221 healthy subjects. The study demonstrated no significant effect on any ECG interval including QTc duration (cardiac repolarization) at doses up to 2.25 mg.

Pharmacokinetics

After intravenous dosing of palonosetron in healthy subjects and cancer patients, 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 (AUC0-∞) are generally dose-proportional over the dose range of 0.3–90 mcg/kg in healthy subjects and in cancer patients. Following single I.V. dose of palonosetron at 3 mcg/kg (0.21 mg/70

kg) to six cancer patients, mean (±SD) maximum plasma concentration was estimated to be 5630 ± 5480 ng/L and mean AUC was 35.8 ± 20.9 h•mcg/L.

Following I.V. administration of palonosetron 0.25 mg once every other day for 3 doses in 11 cancer patients, the mean increase in plasma palonosetron concentration from Day 1 to Day 5 was 42±34%. Following I.V. administration of palonosetron 0.25 mg once daily for 3 days in 12 healthy subjects, the mean (±SD) increase in plasma palonosetron concentration from Day 1 to Day 3 was 110±45%.

After intravenous dosing of palonosetron in patients undergoing surgery (abdominal surgery or vaginal hysterectomy), the pharmacokinetic characteristics of palonosetron were similar to those observed in cancer patients.

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-Shydroxy-palonosetron. These metabolites each have less than 1% of the 5HT3 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

After a single intravenous dose of 10 mcg/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. In healthy subjects, the total body clearance of palonosetron was 0.160 ± 0.035 L/h/kg and renal clearance was 0.067± 0.018 L/h/kg. Mean terminal elimination half-life is approximately 40 hours.

Specific populations

Pediatric Patients

Single-dose I.V. Palonosetron Hydrochloride injection pharmacokinetic data was obtained from a subset of pediatric cancer patients that received 10 mcg/kg or 20 mcg/kg. When the dose was increased from 10 mcg/kg to 20 mcg/kg a dose-proportional increase in mean AUC was observed. Following single dose intravenous infusion of Palonosetron Hydrochloride

injection 20 mcg/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 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 mcg/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.

Pharmacokinetics Parameters in Pediatric Cancer Patients following intravenous infusion of Palonosetron Hydrochloride injection at 20 mcg/kg over 15 min

PK Parameter [a]	**Pediatric Age Group**			
	<2 y	**2 to <6 y**	**6 to <12 y**	**12 to <17 y**
	N=12	**N=42**	**N=38**	**N=44**
C_T[b],ng/L	9025(197)	9414 (252)	16275 (203)	11831 (176)
		N=5	**N=7**	**N=10**
$AUC_{0-\infty}$ h.mcg/L		103.5(40.4)	98.7(47.7)	124.5(19.1)
	N=6	**N=14**	**N=13**	**N=19**
Clearance[c], L/h/kg	0.31(34.7)	0.23(51.3)	0.19(46.8)	0.16(27.8)
vss[c] L/kg	6.08(36.5)	5.29(57.8)	6.26(40.0)	6.20(29.0)

a Geometric Mean (CV) except for t1/2 which is median values .

b C_T is the plasma palonosetron concentration at the end of the 15 minute infusion.

c Clearance and Vss calculated from 10 and 20 mcg/kg and are weight adjusted.

CLINICAL STUDIES

Chemotherapy-Induced Nausea and Vomiting in Adults

Efficacy of single-dose palonosetron injection in preventing acute and delayed nausea and vomiting induced by both moderately and highly emetogenic chemotherapy was studied in three Phase 3 trials and one Phase 2 trial. In these double-blind studies, complete response rates (no emetic episodes and no rescue medication) and other efficacy parameters were assessed through at least 120 hours after administration of chemotherapy. The safety and efficacy of palonosetron in repeated courses of chemotherapy was also assessed.

Moderately Emetogenic Chemotherapy

Two Phase 3, double-blind trials involving 1132 patients compared single-dose I.V. Palonosetron Hydrochloride injection with either single-dose I.V. ondansetron (study 1) or

dolasetron (study 2) given 30 minutes prior to moderately emetogenic chemotherapy including carboplatin, cisplatin ≤ 50 mg/m², cyclophosphamide < 1500 mg/m², doxorubicin > 25 mg/m², epirubicin, irinotecan, and methotrexate > 250 mg/m². Concomitant corticosteroids were not administered prophylactically in study 1 and were only used by 4-6% of patients in study 2. The majority of patients in these studies were women (77%), White (65%) and naïve to previous chemotherapy (54%). The mean age was 55 years.

Highly Emetogenic Chemotherapy

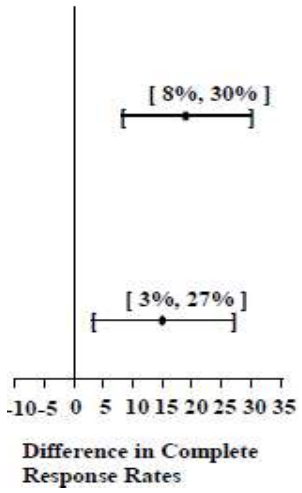
A Phase 2, double-blind, dose-ranging study evaluated the efficacy of single-dose I.V. palonosetron from 0.3 to 90 mcg/kg (equivalent to < 0.1 mg to 6 mg fixed dose) in 161 chemotherapy-naïve adult cancer patients receiving highly-emetogenic chemotherapy (either cisplatin ≥ 70 mg/m² or cyclophosphamide > 1100 mg/m²). Concomitant corticosteroids were not administered prophylactically. Analysis of data from this trial indicates that 0.25 mg is the lowest effective dose in preventing acute nausea and vomiting induced by highly emetogenic chemotherapy.

A Phase 3, double-blind trial involving 667 patients compared single-dose I.V. Palonosetron Hydrochloride injection with single-dose I.V. ondansetron (study 3) given 30 minutes prior to highly emetogenic chemotherapy including cisplatin ≥ 60 mg/m², cyclophosphamide > 1500 mg/m², and dacarbazine. Corticosteroids were co-administered prophylactically before chemotherapy in 67% of patients. Of the 667 patients, 51% were women, 60% White, and 59% naïve to previous chemotherapy. The mean age was 52 years.

Efficacy Results

The antiemetic activity of Palonosetron Hydrochloride injection was evaluated during the acute phase (0-24 hours) delayed phase (24-120 hours) and overall phase (0-120 hours) post-chemotherapy in Phase 3 trials.

Prevention of Acute Nausea and Vomiting (0-24 hours): Complete Response Rates

Chemotherapy	Study	Treatment Group	N[a]	% with Complete Response	p-value[b]	97.5% Confidence Interval Palonosetron Hydrochloride injection minus Comparator[c]
Moderately Emetogenic	1	Palonosetron Hydrochloride injection 0.25 mg	189	81	NS	
		Ondansetron 32 mg I.V.	185	69		
	2	Palonosetron Hydrochloride injection 0.25 mg	189	63	NS	
		Dolasetron 100 mg I.V.	191	53		
Highly Emetogenic	3	Palonosetron Hydrochloride injection 0.25 mg	223	59	NS	
		Ondansetron 32 mg I.V.	221	57		

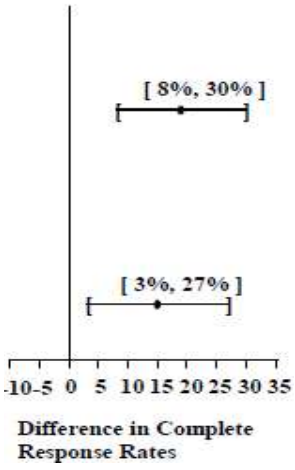
a Intent-to-treat cohort

b 2-sided Fisher's exact test. Significance level at α=0.025.

c These studies were designed to show non-inferiority. A lower bound gr eater than –15% demonstrates non- inferiority between Palonosetron Hydrochloride injection and comparator. These studies show that Palonosetron Hydrochloride injection was effective in the prevention of acute nausea and vomiting associated with initial and repeat courses of moderately and highly emetogenic cancer chemotherapy. In study 3, efficacy was greater when prophylactic corticosteroids were administered concomitantly. Clinical superiority over other 5-HT3 receptor antagonists has not been adequately demonstrated in the acute phase.

Prevention of Delayed Nausea and Vomiting (24-120 hours):

Complete Response Rates

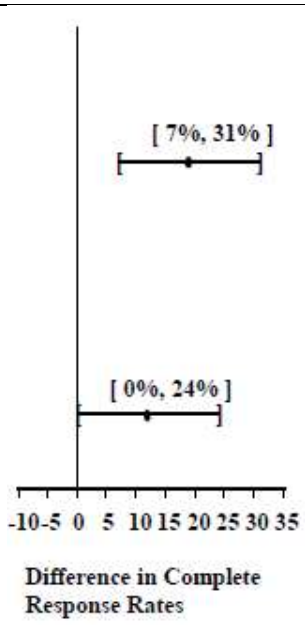
Chemotherapy	Study	Treatment Group	N[a]	% with Complete Response	p-value[b]	97.5% Confidence Interval Palonosetron Hydrochloride injection minus Comparator[c]
Moderately Emetogenic	1	Palonosetron Hydrochloride injection 0.25 mg	189	74	<0.001	
		Ondansetron 32 mg I.V.	185	55		
	2	Palonosetron Hydrochloride injection 0.25 mg	189	54	0.004	
		Dolasetron 100 mg I.V.	191	39		

a Intent-to-tr eat cohort

b 2-sided Fisher's exact test. Significance level at α=0.025.

c These studies were designed to show non-inferiority. A lower bound gr eater than –15% demonstrates non- inferiority between Palonosetron Hydrochloride injection and comparator. These studies show that Palonosetron Hydrochloride injection was effective in the prevention of delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic chemotherapy.

Prevention of Overall Nausea and Vomiting (0-120 hours): Complete Response Rates

Chemotherapy	Study	Treatment Group	N[a]	% with Complete Response	p-value[b]	97.5% Confidence Interval Palonosetron Hydrochloride injection minus Comparator[c]
Moderately Emetogenic	1	Palonosetron Hydrochloride injection 0.25 mg	189	69	<0.001	
		Ondansetron 32 mg I.V.	185	50		
	2	Palonosetron Hydrochloride injection 0.25 mg	189	46	0.021	
		Dolasetron 100 mg I.V.	191	34		

a Intent-to-tr eat cohort

b 2-sided Fisher's exact test. Significance level at α=0.025.

c These studies were designed to show non-inferiority. A lower bound gr eater than –15% demonstrates non-inferiority between Palonosetron Hydrochloride injection and comparator.

These studies show that Palonosetron Hydrochloride injection was effective in the prevention of nausea and vomiting throughout the 120 hours (5 days) following initial and repeat courses of moderately emetogenic cancer chemotherapy.

Chemotherapy-Induced Nausea and Vomiting in Pediatrics

One double-blind, active-controlled clinical trial was conducted in pediatric cancer patients. The total population (N = 327) had a mean age of 8.3 years (range 2 months to 16.9 years) and were 53% male; and 96% white. Patients were randomized and received a 20 mcg/kg (maximum 1.5 mg) intravenous infusion of Palonosetron Hydrochloride injection 30 minutes prior to the start of emetogenic chemotherapy (followed by placebo infusions 4 and 8 hours after the dose of palonosetron) or 0.15 mg/kg of intravenous ondansetron 30 minutes prior to

the start of emetogenic chemotherapy (followed by ondansetron 0.15 mg/kg infusions 4 and 8 hours after the first dose of ondansetron, with a maximum total dose of 32 mg). Emetogenic chemotherapies administered included doxorubicin, cyclophosphamide (<1500 mg/m^2), ifosfamide, cisplatin, dactinomycin, carboplatin, and daunorubicin. Adjuvant corticosteroids, including dexamethasone, were administered with chemotherapy in 55% of patients.

Complete Response in the acute phase of the first cycle of chemotherapy was defined as no vomiting, no retching, and no rescue medication in the first 24 hours after starting chemotherapy. Efficacy was based on demonstrating non-inferiority of intravenous palonosetron compared to intravenous ondansetron. Non-inferiority criteria were met if the lower bound of the 97.5% confidence interval for the difference in Complete Response rates of intravenous palonosetron minus intravenous ondansetron was larger than -15%. The non-inferiority margin was 15%.

Efficacy Results

Intravenous Palonosetron Hydrochloride injection 20 mcg/kg (maximum 1.5 mg) demonstrated non-inferiority to the active comparator during the 0 to 24 hour time interval.

Prevention of Acute Nausea and Vomiting (0-24 hours):

Complete Response Rates

I.V. Palonosetron Hydrochloride injection 20 mcg/kg (N=165)	**I.V. Ondansetron 0.15 mg/kg x 3 (N=162)**	**Difference [97.5% Confidence Interval]*: I.V. Palonosetron Hydrochloride injection minus I.V. Ondansetron Comparator**
59.4%	58.6%	0.36% [-11.7%, 12.4%]

* To adjust for multiplicity of treatment groups, a lower-bound of a 97.5% confidence interval was used to compare to -15%, the negative value of the non-inferiority margin.

In patients that received Palonosetron Hydrochloride injection at a lower dose than the recommended dose of 20 mcg/kg, non-inferiority criteria were not met.

Postoperative Nausea and Vomiting

In one multicenter, randomized, stratified, double-blind, parallel-group, phase 3 clinical study (Study 1), palonosetron was compared with placebo for the prevention of PONV in 546 patients undergoing abdominal and gynecological surgery. All patients received general

anesthesia. Study 1 was a pivotal study conducted predominantly in the US in the out-patient setting for patients undergoing elective gynecologic or abdominal laparoscopic surgery and stratified at randomization for the following risk factors: gender, non-smoking status, history of post-operative nausea and vomiting and/or motion sickness.

In Study 1 patients were randomized to receive palonosetron 0.025 mg, 0.050 mg or 0.075 mg or placebo, each given intravenously immediately prior to induction of anesthesia. The antiemetic activity of palonosetron was evaluated during the 0 to 72 hour time period after surgery.

Of the 138 patients treated with 0.075 mg palonosetron in Study 1 and evaluated for efficacy, 96% were women; 66% had a history of PONV or motion sickness; 85% were non-smokers. As for race, 63% were White, 20% were Black, 15% were Hispanic, and 1% were Asian. The age of patients ranged from 21 to 74 years, with a mean age of 37.9 years. Three patients were greater than 65 years of age

Co-primary efficacy measures were Complete Response (CR) defined as no emetic episode and no use of rescue medication in the 0-24 and in the 24-72 hours postoperatively.

Secondary efficacy endpoints included:

- Complete Response (CR) 0-48 and 0-72 hours
- Complete Control (CC) defined as CR and no more than mild nausea

Severity of nausea (none, mild, moderate, severe)

The primary hypothesis in Study 1 was that at least one of the three palonosetron doses were superior to placebo.

Results for Complete Response in Study 1 for 0.075 mg palonosetron versus placebo.

Prevention of Postoperative Nausea and Vomiting: Complete Response (CR), Study 1, Palonosetron 0.075 mg Vs Placebo

Treatment	**n/N (%)**	**Palonosetron Vs Placebo**	
		Δ	**p-value***
Co-primary Endpoints			
CR 0-24 hours			
Palonosetron	59/138 (42.8%)	16.8%	0.004
Placebo	35/135 (25.9%)		
CR 24-72 hours			
Palonosetron	67/138 (48.6%)	7.8%	0.188
Placebo	55/135 (40.7%)		

* To reach statistical significance for each co-primary endpoint, the required significance limit for the lowest p-value was p<0.017.

Δ Difference (%): palonosetron 0.075 mg minus placebo

Palonosetron 0.075 mg reduced the severity of nausea compared to placebo. Analyses of other secondary endpoints indicate that palonosetron 0.075mg was numerically better than placebo, however, statistical significance was not formally demonstrated.

A phase 2 randomized, double-blind, multicenter, placebo-controlled, dose ranging study was performed to evaluate I.V. palonosetron for the prevention of post-operative nausea and vomiting following abdominal or vaginal hysterectomy. Five I.V. palonosetron doses (0.1, 0.3, 1.0, 3.0 and 30 μg/kg) were evaluated in a total of 381 intent-to-treat patients. The primary efficacy measure was the proportion of patients with CR in the first 24 hours after recovery from surgery. The lowest effective dose was palonosetron 1 μg/kg (approximately 0.075 mg) which had a CR rate of 44% versus 19% for placebo, p=0.004. Palonosetron 1 μg/kg also significantly reduced the severity of nausea versus placebo, p=0.009.

6. Pharmaceutical particulars

6.1 List of excipients

Mannitol USP, Edetate Disodium USP, Sodium Citrate Dihydrate (Tri Sodium Citrate Dihydrate) USP, Citric acid Monohydrate USP, Sodium Hydroxide USP-NF, Hydrochloric Acid USP-NF and Water for Injection IH

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 Months.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

Glass Vials: 5 mL clear Tubular glass vial.

6.6 Special precautions for disposal and other handling

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

7. Marketing authorization holder

7.1 Name and Address of Manufacturer

Name: **Aspiro Pharma Limited.**

Company name: **Aspiro Pharma Limited.**

Business Address: Survey No. 321, Biotech Park, Phase III, Karkapatla, Markook Mandal, Siddipet District, Telangana (S)-502281, INDIA.

Country: INDIA

Phone: +91 9959644022, 9959644077

Fax: --

E-Mail: vinodkumar.u@aspiropharma.com

7.2 Name and Address of Principal

Name : Aspiro Pharma Limited,

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Country : INDIA

Telephone : +9140 23704923/24/25, +91 40 23707171/7272/7744

Telephone : +91-40-23704035/23813359

E-Mail : vinodkumar.u@aspiropharma.com

8. REGISTRATION NUMBER

Not applicable

9. CATEGORY FOR DISTRIBUTION

PP – 'Prescription preparation'.

10. DATE OF PUBLICATION OF THIS PACKAGE INSERT

Not applicable