PALOXI®

Composition:
Each ml of injection contain
Palonosetron (as hydrochloride)..... 50 micrograms

Description:
Paloxi® 0.05 mg/mL contains 0.25 mg of palonosetron as base in a non-preserved, aqueous based formulation. It is available commercially as a 5 mL sterile solution and administered by intravenous injection. There are no overages in the formulation.

Pharmacology
Pharmacodynamic properties
Pharmacotherapeutic group: Antiemetic and antinauseants, serotonin ($5HT_3$)antagonists. ATC code: A04AA05

Palonosetron ia a selective high-affinity receptor antagonist of the $5HT_3$ receptor.
In two randomised, double-blind studies with a total of 1.132 patients receiving moderately emetogenic chemotherapy that included cisplatin ≤ 50 mg/m^2, carboplatin, cyclophosphamide ≤ 1,500 mg/m^2 and doxorubicin > 25 mg/m^2 palonosetron 250 micrograms and 750 micrograms were compared with ondansetron 32 mg (half-life 4 hours) or dolasetron 100 mg (half-life 7.3 hours) administered intravenously on Day 1, without dexamethasone.
In a randomised, double-blind study with a total of 667 patients receiving highly emetogenic chemotherapy that included cisplatin ≥ 60 mg/m^2, cyclophophamide > 1,500 mg/m^2 and dacarbazine, palonosetron 250 micrograms and 750 micrograms were compared with ondansetron 32 mg administered intravenously on Day 1. Dexamethasone was administered prophylactically before chemotherapy in 67% of patients.

The pivotal studies were not designed to assess efficacy of palonosetron in delayed onset nausea and vomiting. The antiemetic activity was observed during 0-24 hours, 24-120 hours and 0-120 hours. Results for the studies on moderately emetogenic chemotherapy and for the study on highly emetogenic chemotherapy are summarised in the following tables.

Palonosetron was non-inferior versus the comparators in the acute phase of emesis both in moderately and highly emetogenic setting.

Although comparative efficacy of palonosetron in multiple cycles has not been demonstrated in controlled clinical trials, 875 patients enrolled in the three phase 3 trials continued in an open label safety study and were treated with palonosetron 750 micrograms for up to 9 additional cycles of chemotherapy. The overall safety was maintained during all cycles.

Table 1:	**Percentage of patients [a] responding by treatment group snd phase in the Moderately Emetogenic Chemotherapy study versus ondansetron**			
	Paloxi 250 micrograms (n= 189)	Ondansetron 32 milligrams (n= 185)	Delta	
	%	%	%	

Complete Response (No Emesis and No Rescue Medication)				97.5% CI [b]
0 - 24 hours	81.0	68.6	12.4	[1.8%, 22.8%]
24 - 120 hours	74.1	55.1	19.0	[7.5%, 30.3%]
0 - 120 hours	69.3	50.3	19.0	[7.4%, 30.7%]
Complete Control (Complete Response and No More Than Mild Nausea)				**p-value [c]**
0 - 24 hours	76.2	65.4	10.8	NS
24 - 120 hours	66.7	50.3	16.4	0.001
0 - 120 hours	63.0	44.9	18.1	0.001
No Nausea (Likert Scale)				**p-value [c]**
0 - 24 hours	60.3	56.8	3.5	NS
24 - 120 hours	51.9	39.5	12.4	NS
0 - 120 hours	45.0	36.2	8.8	NS

[a] Intent-to-treat cohort

[b] The study was designed to show non-inferiority. A lower bound greater than-15% demonstrates non-inferiority between Paloxi and comparator

[c] Chi-square test. Significance level at α = 0.05

Table 2:	**Percentage of patients [a] responding by treatment group and phase in the Moderately Emetogenic Chemotherapy study versus dolasetron**			
	Paloxi 250 micrograms (n= 185)	Dolasetron 100 miligrams (n= 191)	Delta	
	%	%	%	
Complete Response (No Emesis and No Rescue Medication)				**97.5% CI [b]**
0 - 24 hours	63.0	52.9	10.1	[-1.7%, 21.9%]
24 - 120 hours	54.0	38.7	15.3	[3.4%, 27.1%]
0 - 120 hours	46.0	34.0	12.0	[0.3%, 23.7%]
Complete Control (Complete Response and No More Than Mild Nausea)				**p-value [c]**
0 - 24 hours	57.1	47.6	9.5	NS
24 - 120 hours	48.1	36.1	12.0	0.018
0 - 120 hours	41.8	30.9	10.9	0.027
No Nausea (Likert Scale)				**p-value [c]**
0 - 24 hours	48.7	41.4	7.3	NS
24 - 120 hours	41.8	26.2	15.6	0.001
0 - 120 hours	33.9	22.5	11.4	0.014

[a] Intent-to-treat cohort

[b] The study was designed to show non-inferiority. A lower bound greater than-15% demonstartes

non-inferiority between Paloxi and comparator

[c] Chi-square test. Significance level at α = 0.05

Table 3:	**Percentage of patients [a] responding by treatment group snd phase in the Highly Emetogenic Chemotherapy study versus ondansetron**			
	Paloxi 250 micrograms (n= 223)	Ondansetron 32 miligrams (n= 221)	Delta	
	%	%	%	
Complete Response (No Emesis and No Rescue Medication)				**97.5% CI [b]**
0 - 24 hours	59.2	57.0	2.2	[-8.8%, 13.1%]
24 - 120 hours	45.3	38.9	6.4	[-4.6%, 17.3%]
0 - 120 hours	40.8	33.0	7.8	[-2.9%, 18.5%]
Complete Control (Complete Response and No More Than Mild Nausea)				**p-value [c]**
0 - 24 hours	56.5	51.6	4.9	NS
24 - 120 hours	40.8	35.3	5.5	NS
0 - 120 hours	37.7	29.0	8.7	NS
No Nausea (Likert Scale)				**p-value [c]**
0 - 24 hours	53.8	49.3	4.5	NS
24 - 120 hours	35.4	32.1	3.3	NS
0 - 120 hours	33.6	32.1	1.5	NS

[a] Intent-to-treat cohort

[b] The study was designed to show non-inferiority. A lower bound greater than-15% demonstrates non-inferiority between Paloxi and comparator

[c] Chi-square test. Significance level at α = 0.05

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 (Cmax) and area under the concentration-time curve (AUC-∞) are generally dose-proportional over the dose range of 0.3-90 µg/kg in healthy subjects and in cancer patients.

Distribution

Palonosetron at the recommended dose is widely distributed in the body with a volume of distribution of approximately 6.9 to 7.91/kg. Approximately 62% of palonosetron is bound to plasma proteins.

Metabolism

Palonosetron is eliminated by dual route, about 40 % eliminated through the kidney and with approximately 50 % metobolised form two primary metobolites, which have less than 1 % of the $5HT_3$ receptor antagonist activity of palonosetron. *In vitro* metobolism 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 cinically 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: 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 patients: no pharmacokinetic data are available in patients below 18 years of age.
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.

Preclinical safety data

Preclinical effects were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.
Nonclinical studies indicate that palonosetron, only at very high concentrations, may block ion channels involved in ventricular de- and re-polarisation and prolong action potential duration. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy embryonal/foetal development, parturition or postnatal development. Only limited data from animal studies are available regarding the placental transfer (see section pregnancy and lactation). Palonosetron is not mutagenic. High doses of palonosetron (each dose causing at least 30 times the human therapeutic exposure) applied daily for two years caused an increased rate of liver tumours, endocrine neoplasms (in thyroid, pituitary, pancreas, adrenal medulla) and skin tumours in rats but not in mice. The underlying mechanisms are not fully understood, but because of the high doses employed and since Paloxi is intended for single application in humans, these findings are not considered relevant for clinical use.

Indications

Paloxi ® is indicated for:
The prevention of acute nausea and vomiting associated with highly emetogenic cancer chemotherapy
and
the prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy.

Posology and method of administration
For intravenous use:
Adults:

250 micrograms palonosetron administered as a single intravenous bolus approximately 30 minutes before the start of chemotherapy. Paloxi should be injected over 30 seconds
Repeated dosing of Paloxi within a seven day interval is not recommended.
The efficacy of Paloxi 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.

Elderly:

No dosage adjustment is necessary for the elderly.

Children and adolescents:

Use in patients under 18 years of age is not recommended until further data become available.

Hepatic impaired patients

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

Renal impaired patients

No dose adjustment is necessary for patients with impaired renal function.
No data are available for patients with end stage renal disease undergoing haemodialysis.

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 signs 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. However, as for other 5-HT_3 antagonists, caution should be exercised in the concomitant use of palonosetron with medicinal products that increase the QT interval or in patients who have or are likely to develop prolongation of the QT interval.

Pregnancy and lactation
Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. Only limited data from animal studies are available regarding the placental transfer (see preclinical safety data).
There is no experience of palonosetron in human pregnancy so palonosetron should not be used in pregnant women unless it is considered essential by the physician. As there are no data

concerning palonosetron excretion in breast milk, breast-feeding should be discontinued during therapy.

Adverse Effects

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

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

In the clinical studies the following adverse reactions (ARs) were observed as possibly or probably related to Paloxi. These were classified as common (between 1% and 10%) or uncommon (between 0.1% and 1%).

System Organ Class	Common ARs (>1/100 to <1/10)	Uncommon ARs (>1/1,000 to <1/100)
Metabolism and nutrition disorders		Hyperkalaemia, metabolic disorders, hypocalcaemia, 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 arrhytmia, supraventricular extrasystoles
Vascular disorders		Hypotension, hypertension, vein discolouration, vein distended
Respiratory, thoracic and mediatinal disorders		Hiccups
Gastrointestinal disorders	Constipation Diarrhoea	Dyspepsia, abdominal pain, abdominal pain upper, dry mouth, flatulence
Hepato-biliary 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
Investigations		Elevated transaminases, hypokalaemia electrocardiogram QT prolonged

Very rare cases (<1/10,000) of hypersensitivity reactions and injection site reactions (burning, induration, discomfort and pain) were reported from post-marketing experience.

Overdose
No case of overdose has been reported.
Doses of up to 6 mg have been used in clinical trials. The highest dose group showed a similar incidence of adverse events compared to the other dose groups and no dose response effects were observed. In the unlikely event of overdose with Paloxi, 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 Paloxi overdose.

Contraindications
Hypersensitivity to the active substance or to any of the excipients.

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).

Corticosteroid: palonosetron has been administered safely with corticosteroids.

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

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

Storage Conditions
Store at room temperature (below 30^{o}C).
Upon opening of the vial, any unused solution should be discarded.

Shelf life
3 years

Presentation
Paloxi ® 0.25 mg/5 ml: Box of 1 vial @ 5 ml Reg No. DKI

Manufactured by:
Cardinal Health, Albuqurque, NM, USA
For
Helsinn Birex Pharmaceuticals Ltd.
Damastown, Mulhuddart
Dublin 15
Ireland

Imported and Marketed by:
PT. KALBE FARMA Tbk., Bekasi-Indonesia
Under Licence of:
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