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1. NAME OF THE MEDICINAL PRODUCT

Paloxi® Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 0.5 mg (=500 micrograms) palonosetron (as hydrochloride).

Excipient(s):
Each capsule contains 7 mg sorbitol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Soft capsule.

Plain, light beige, opaque, round to oval, soft gelatine capsules, filled with a clear yellowish solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Paloxi is indicated in adults for the prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy.

4.2 Posology and method of administration

Paloxi should be used only before chemotherapy administration.

Posology

Adults

500 micrograms palonosetron administered orally approximately one hour before the start of chemotherapy.

Elderly population

No dose adjustment is necessary for the elderly.

Paediatric population

The safety and efficacy of Paloxi in children have not been established. Currently available data are described in section 5.1 and section 5.2, but no recommendation on posology can be made.

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 oral use.
Paloxi can be taken with or without food.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 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 QT corrected (QTc) interval. A specific thorough QT/QTc study was conducted in healthy volunteers for definitive data demonstrating the effect of palonosetron on QT/QTc. (see section 5.1).

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.

Paloxi should not be used to prevent or treat nausea and vomiting in the days following chemotherapy if not associated with another chemotherapy administration.

Paloxi contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not take this medicinal product. Paloxi capsules may also contain a trace of lecithin derived from soya. Therefore, patients with known hypersensitivity to peanut or soya, should be monitored closely for signs of an allergic reaction.

4.5 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 medicinal products
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-HT3 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.

4.6 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 from animal studies are available regarding the placental transfer (see section 5.3). 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.

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.

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 at a dose of 500 micrograms (total 161 patients) the most frequently observed adverse reaction, at least possibly related to Paloxi, was headache (3.7 %).

In the clinical studies the following adverse reactions (ARs) were observed as possibly or probably related to Paloxi. These were classified as common (≥1/100 to <1/10) or uncommon (≥1/1,000 to <1/100).

System Organ Class	Common ARs	Uncommon ARs
Psychiatric disorders		Insomnia
Nervous system disorders	Headache	
Eye disorders		Eye swelling
Cardiac disorders		Atrioventricular block first degree, atrioventricular block second degree
Respiratory, thoracic and mediastinal disorders		Dyspnoea
Gastrointestinal disorders		Constipation, nausea
Musculoskeletal and connective tissue disorders		Myalgia
Investigations		Blood bilirubin increased

In post marketing very rare cases (<1/10,000) of hypersensitivity reactions occurred with palonosetron solution for injection for intravenous use.
Adverse reactions with unknown frequency: dizziness, somnolence, fatigue.

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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

https://sideeffects.health.gov.il

4.9 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 reactions 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 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.
In a multicentre, randomised, double-blind active control clinical trial of 635 patients set to receive moderately emetogenic cancer chemotherapy. A single-dose of 250 mcg, 500 mcg, or 750 mcg oral palonosetron capsules given one hour prior to moderately emetogenic chemotherapy was compared to a single-dose of 250 mcg intravenous Paloxi given 30 minutes

prior to chemotherapy. Patients were randomised to either dexamethasone or placebo in addition to their assigned treatment. The majority

of patients in the study were women (73 %), white (69 %), and naïve to previous chemotherapy (59 %). The antiemetic activity was observed during 0-24 hours, 24-120 hours and 0-120 hours. Efficacy was based on demonstrating non-inferiority of oral palonosetron doses compared to the approved intravenous formulation. Non-inferiority criteria were met if the lower bound of the two-sided 98.3 % confidence interval for the difference in complete response rates of oral palonosetron dose minus approved intravenous formulation was larger than -15 %. The non-inferiority margin was 15 %.

As shown in Table 1, oral Paloxi capsules 500 micrograms demonstrated non-inferiority to the active comparator during the 0 to 24 hour and 0 to 120 hour time intervals; however, for the 24 to 120 hour time period, non-inferiority was not shown.

Although comparative efficacy of palonosetron in multiple cycles has not been demonstrated in controlled clinical trials, 217 patients were enrolled in a multicentre, open label safety study and were treated with palonosetron capsules 750 micrograms for up to 4 cycles of chemotherapy in a total of 654 chemotherapy cycles. Approximately 74 % of patients also received single dose oral or intravenous dexamethasone 30 minutes before chemotherapy. Complete Response was not formally evaluated for the repeat cycle application. However, in general the antiemetic effect for the 0-24 hour interval was similar throughout the consecutively repeated cycles and the overall safety was maintained during all cycles.

Table 1: Proportion of patients[a] responding by treatment group and phase

	Paloxi Oral 500 micrograms (n=160)	Paloxi Intravenous 250 micrograms	Delta	
	%	%	%	
Complete Response (No Emesis and No Rescue Medication)				**98.3 % CI[b]**
0-24 hours	76.3	70.4	5.9	[-6.5 %, 18.2 %]
24-120 hours	62.5	65.4	-2.9	[-16.3 %, 10.5 %]
0-120 hours	58.8	59.3	-0.5	[-14.2 %, 13.2 %]
Complete Control (Complete Response and No More Than Mild Nausea)				**p-value[c]**
0-24 hours	74.4	68.5	5.9	NS
24-120 hours	56.3	62.3	-6.0	NS
0-120 hours	52.5	56.2	-3.7	NS
No Nausea (Likert Scale)				**p-value[c]**
0-24 hours	58.8	57.4	1.4	NS
24-120 hours	49.4	47.5	1.9	NS
0-120 hours	45.6	42.6	3.0	NS

[a] Intent-to-treat cohort

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

[c] Chi-square test. Significance levels at alpha 0.0167 (adjusted for multiple comparisons).

In non-clinical studies palonosetron possesses the ability to block ion channels involved in ventricular de- and re-polarisation and to prolong action potential duration.
The effect of palonosetron on QTc interval was evaluated in a double blind, randomised, parallel, placebo and positive (moxifloxacin) controlled trial in adult men and women. The objective was to evaluate the ECG effects of IV administered palonosetron at single doses of 0.25, 0.75 or 2.25 mg in 221 healthy subjects. The study demonstrated no effect on QT/QTc interval duration as well as any other ECG interval at doses up to 2.25 mg. No clinically significant changes were shown on heart rate, atrioventricular (AV) conduction and cardiac repolarization.

Paediatric population

Prevention of Chemotherapy Induced Nausea and Vomiting (CINV):

The safety and efficacy of Palonosetron i.v at single doses of 3µg/kg and 10µg/kg was investigated in the first clinical study in 72 patients in the following age groups, >28 days to 23 months (12 patients), 2 to 11 years (31 patients), and 12 to 17 years of age (29 patients), receiving highly or moderately emetogenic chemotherapy. No safety concerns were raised at either dose level. The primary efficacy variable was the proportion of patients with a complete response (CR, defined as no emetic episode and no rescue medication) during the first 24 hours after the start of chemotherapy administration. Efficacy after palonosetron 10 µg/kg compared to palonosetron 3µg/kg was 54.1% and 37.1% respectively.

The efficacy of Paloxi for the prevention of chemotherapy-induced nausea and vomiting in paediatric cancer patients was demonstrated in a second non-inferiority pivotal trial comparing a single intravenous infusion of palonosetron versus an i.v. ondansetron regimen. A total of 493 paediatric patients, aged 64 days to 16.9 years, receiving moderately (69.2%) or highly emetogenic chemotherapy (30.8%) were treated with palonosetron 10 µg/kg (maximum 0.75 mg), palonosetron 20 µg/kg (maximum 1.5 mg) or ondansetron (3 x 0.15 mg/kg , maximum total dose 32 mg) 30 minutes prior to the start of emetogenic chemotherapy during Cycle 1. Most patients were non-naïve to chemotherapy (78.5%) across all treatment groups. 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. The primary efficacy endpoint was Complete Response in the acute phase of the first cycle of chemotherapy, 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%. In the palonosetron 10 µg/kg, 20 µg/kg and ondansetron groups, the proportion of patients with $CR_{0\text{-}24h}$ was 54.2%, 59.4% and 58.6%. Since the 97.5% confidence interval (stratum adjusted Mantel-Haenszel test) of the difference in $CR_{0\text{-}24h}$ between palonosetron 20 µg/kg and ondansetron was [- 11.7%, 12.4%], the 20 µg/kg palonosetron dose demonstrated non-inferiority to ondansetron.

While this study demonstrated that paediatric 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 (see section 4.8). Pharmacokinetic information is provided in section 5.2.

Prevention of Post Operative Nausea and Vomiting (PONV):

Two paediatric trials were performed. The safety and efficacy of Palonosetron i.v at single doses of 1µg/kg and 3µg/kg was compared in the first clinical study in 150 patients in the following age groups, >28 days to 23 months (7 patients), 2 to 11 years (96 patients), and 12 to 16 years of age (47 patients) undergoing elective surgery. No safety concerns were raised in either treatment group. The proportion of patients without emesis during 0-72 hours post-operatively was similar after palonosetron 1 µg/kg or 3 µg/kg (88% vs 84%).

The second paediatric trial was a multicenter, double-blind, double-dummy, randomised, parallel group, active control, single-dose non-inferiority study, comparing i.v. palonosetron (1 µg/kg, max 0.075 mg) versus i.v. ondansetron. A total of 670 paediatric surgical patients participated, age 30 days to 16.9 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 No new safety concerns were raised in either treatment group.

Please see section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

Absorption
Following oral administration, palonosetron is well absorbed with its absolute bioavailability reaching 97 %. After single oral doses using buffered solution mean maximum palonosetron concentrations (C_{max}) and area under the concentration-time curve (AUC0-∞) were dose proportional over the dose range of 3.0 to 80 µg/kg in healthy subjects.

In 36 healthy male and female subjects given a single oral dose of palonosetron capsules 500 micrograms, maximum plasma palonosetron concentration (C_{max}) was 0.81 ± 0.17 ng/ml (mean ± SD) and time to maximum concentration (Tmax) was 5.1 ± 1.7 hours. In female subjects (n=18), the mean AUC was 35 % higher and the mean C_{max} was 26 % higher than in male subjects (n=18).
In 12 cancer patients given a single oral dose of palonosetron capsules 500 micrograms one hour prior to chemotherapy, C_{max} was 0.93 ± 0.34 ng/ml and Tmax was 5.1 ± 5.9 hours. The AUC was 30 % higher in cancer patients than in healthy subjects.

A high fat meal did not affect the C_{max} and AUC of oral palonosetron. Therefore, Paloxi capsules may be taken without regard to meals.

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
Following administration of a single oral 750 micrograms dose of [^{14}C]-palonosetron to six healthy subjects, 85 % to 93 % of the total radioactivity was excreted in urine, and 5 % to 8 % was eliminated in feces. The amount of unchanged palonosetron excreted in the urine represented approximately 40 % of the administered dose. In healthy subjects given palonosetron capsules 500 micrograms, the terminal elimination half-life (t½) of palonosetron was 37 ± 12 hours (mean ± SD), and in cancer patients, t½ was 48 ± 19 hours. After a single-dose of approximately 0.75 mg intravenous palonosetron, the total body clearance of palonosetron in healthy subjects was 160 ± 35 ml/h/kg (mean ± SD) and renal clearance was 66.5 ± 18.2 ml/h/kg.

Pharmacokinetics in special populations

Elderly people
Age does not affect the pharmacokinetics of palonosetron. No dose adjustment is necessary in elderly patients.

Gender
Gender does not affect the pharmacokinetics of palonosetron. No dose adjustment is necessary based on gender.

Paediatric patients

Single-dose i.v. Paloxi pharmacokinetic data was obtained from a subset of paediatric cancer patients (n=280) that received 10 µg/kg or 20 µg/kg. When the dose was increased from10 µg/kg to 20 µg/kg a dose-proportional increase in mean AUC was observed. Following single dose intravenous infusion of Paloxi 20 µg/kg, peak plasma concentrations (C_T) 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.

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.

Table 2: Pharmacokinetic Parameters in Paediatric Cancer Patients following intravenous infusion of Paloxi at 20 µg/kg over 15 min and in Adult Cancer Patients receiving 3 and 10 µg/kg palonosetron doses via intravenous bolus.

	Paediatric Cancer Patients[a]				**Adults Cancer Patients[b]**	
	<2 y	**2 to <6 y**	**6 to <12 y**	**12 to <17 y**	**3.0 µg/kg**	**10 µg/kg**
	N=3	**N=5**	**N=7**	**N=10**	**N=6**	**N=5**
$AUC_{0-\infty}$, h·µg/L	69.0 (49.5)	103.5 (40.4)	98.7 (47.7)	124.5 (19.1)	35.8 (20.9)	81.8 (23.9)
$t_{½}$, hours	24.0	28	23.3	30.5	56.4 (5.81)	49.8 (14.4)
	N=6	**N=14**	**N=13**	**N=19**	**N=6**	**N=5**
Clearance [c], L/h/kg	0.31 (34.7)	0.23 (51.3)	0.19 (46.8)	0.16 (27.8)	0.10 (0.04)	0.13 (0.05)
Volume of distribution [c, d], L/kg	6.08 (36.5)	5.29 (57.8)	6.26 (40.0)	6.20 (29.0)	7.91 (2.53)	9.56 (4.21)

[a] PK parameters expressed as Geometric Mean (CV) except for $T_{½}$ which is median.
[b] PK parameters expressed as Arithmetic mean (SD)
[c] Clearance and Volume of distribution in paediatric patients were calculated weight-adjusted from both 10 µg/kg and 20 µg /kg dose groups combined. In adults, different dose levels are indicated in column title.
[d] Vss is reported for paediatric cancer patients, whereas Vz is reported for adult cancer patients.

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 dose 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.

5.3 Preclinical safety data

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

Non-clinical 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 4.6).

Palonosetron is not mutagenic. High doses of palonosetron (each dose causing at least 15 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycerol monocaprylocaprate, gelatin, sorbitol blend (sorbitol, sorbitan, glycerin), glycerin, purified water, polyglyceryl oleate, titanium dioxide, butylated hydroxyanisole.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

Polyamide/aluminium/PVC blister containing one or five soft capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MANUFACTURER

Helsinn Birex Pharmaceuticals Ltd., Dublin, Ireland

8. REGISTRATION HOLDER
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Registration number: 162-48-35784