

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Aloxi 250 micrograms solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution contains 50 micrograms palonosetron (as hydrochloride).

Each vial of 5 ml of solution contains 250 micrograms palonosetron (as hydrochloride).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Aloxi is indicated in adults for:

- 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.

Aloxi is indicated in paediatric patients 1 month of age and older for:

- the prevention of acute nausea and vomiting associated with highly emetogenic cancer chemotherapy and prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy.

4.2 Posology and method of administration

Aloxi should be used only before chemotherapy administration. This medicinal product should be administered by a healthcare professional under appropriate medical supervision.

Posology

Adults

250 micrograms palonosetron administered as a single intravenous bolus approximately 30 minutes before the start of chemotherapy. Aloxi should be injected over 30 seconds.

The efficacy of Aloxi 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 people

No dose adjustment is necessary for the elderly.

Paediatric population

Children and Adolescents (aged 1 month to 17 years):

20 micrograms/kg (the maximum total dose should not exceed 1500 micrograms) palonosetron administered as a single 15 minute intravenous infusion beginning approximately 30 minutes before the start of chemotherapy.

The safety and efficacy of Aloxi in children aged less than 1 month have not been established. No data are available. There are limited data on the use of Aloxi in the prevention of nausea and vomiting in children under 2 years of age.

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.

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 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-HT₃ 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-HT₃-antagonist administration.

There have been reports of serotonin syndrome with the use of 5-HT₃ 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.

Aloxi 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'.

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 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-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. 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.

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 ($\geq 1/100$ to $< 1/10$) or uncommon ($\geq 1/1,000$ 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 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

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 the national reporting system listed in Appendix V.

4.9 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 Aloxi, 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 Aloxi overdose.

Paediatric population

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiemetics and antinauseants, serotonin (5HT₃) antagonists. ATC code: A04AA05

Palonosetron is a selective high-affinity receptor antagonist of the 5HT₃ receptor.

In two randomised, double-blind studies with a total of 1,132 patients receiving moderately emetogenic chemotherapy that included cisplatin ≤ 50 mg/m², carboplatin, cyclophosphamide $\leq 1,500$ mg/m² and doxorubicin >25 mg/m², 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/m², cyclophosphamide $> 1,500$ mg/m² 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 studies, 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 and phase in the Moderately Emetogenic Chemotherapy study versus ondansetron

	Aloxi 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 Aloxi and comparator.

^c Chi-square test. Significance level at $\alpha=0.05$.

Table 2: Percentage of patients^a responding by treatment group and phase in the Moderately Emetogenic Chemotherapy study versus dolasetron

	Aloxi 250 micrograms (n= 185) %	Dolasetron 100 milligrams (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 % demonstrates non-inferiority between Aloxi and comparator.

^c Chi-square test. Significance level at $\alpha=0.05$.

Table 3: Percentage of patients^a responding by treatment group and phase in the Highly Emetogenic Chemotherapy study versus ondansetron

	Aloxi 250 micrograms (n= 223)	Ondansetron 32 milligrams (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 Aloxi and comparator.

^c Chi-square test. Significance level at $\alpha=0.05$.

The effect of palonosetron on blood pressure, heart rate, and ECG parameters including QTc were comparable to ondansetron and dolasetron in CINV clinical studies. 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 repolarisation.

Paediatric population

Prevention of Chemotherapy Induced Nausea and Vomiting (CINV):

The safety and efficacy of Palonosetron i.v at single doses of 3 µg/kg and 10 µg/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 Aloxi 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/m²), 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_{0-24h} was 54.2%, 59.4% and 58.6%. Since the 97.5% confidence interval (stratum adjusted Mantel-Haenszel test) of the difference in CR_{0-24h} 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 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-∞}) are generally dose-proportional over the dose range of 0.3–90 µg/kg in healthy subjects and in cancer patients.

Following intravenous administration of palonosetron 0.25 mg once every other day for 3 doses in 11 testicular cancer patients, the mean (± SD) increase in plasma concentration from Day 1 to Day 5 was 42 ± 34 %. After intravenous 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 %.

Pharmacokinetic simulations indicate that the overall exposure (AUC_{0-∞}) 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 5HT₃ 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 [¹⁴C]-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

Single-dose i.v. Aloxi 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 from 10 µg/kg to 20 µg/kg a dose-proportional increase in mean AUC was observed. Following single dose intravenous infusion of Aloxi 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 4: Pharmacokinetic Parameters in Paediatric Cancer Patients following intravenous infusion of Aloxi 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-∞} , 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 _{1/2} , 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_{1/2} 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 V_{ss} is reported for paediatric cancer patients, whereas V_z 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 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.

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 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 Aloxi is intended for single application in humans, these findings are not considered relevant for clinical use.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Disodium edetate
Sodium citrate
Citric acid monohydrate
Sodium hydroxide (for pH adjustment)
Hydrochloric acid (for pH adjustment)
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

5 years.
Upon opening of the vial, use immediately and discard any unused solution.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Type I glass vial with chlorobutyl siliconised rubber stopper and aluminium cap.
Available in packs of 1 vial containing 5 ml of solution.

6.6 Special precautions for disposal

Single use only, any unused solution should be discarded.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Helsinn Birex Pharmaceuticals Ltd.
Damastown
Mulhuddart
Dublin 15
Ireland

8. MARKETING AUTHORISATION NUMBER

EU/1/04/306/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 March 2005

Date of latest renewal: 23 March 2010

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>

1. NAME OF THE MEDICINAL PRODUCT

Aloxi 500 micrograms soft capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 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

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

4.2 Posology and method of administration

Aloxi 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 Aloxi 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.
Aloxi 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-HT₃ 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-HT₃-antagonist administration.

There have been reports of serotonin syndrome with the use of 5-HT₃ 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.

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

Aloxi contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not take this medicinal product. Aloxi 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 Aloxi, was headache (3.7 %).

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

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 the national reporting system listed in Appendix V.

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 Aloxi, 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 Aloxi overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiemetics and antinauseants, Serotonin (5HT₃) antagonists, ATC code: A04AA05

Palonosetron is a selective high-affinity receptor antagonist of the 5HT₃ 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 Aloxi 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 Aloxi 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

	Aloxi Oral 500 micrograms (n=160)	Aloxi Intravenous 250 micrograms (n=162)	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 than -15 % demonstrates non-inferiority between Aloxi oral and comparator Aloxi 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 Aloxi 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/m²), 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_{0-24h} was 54.2%, 59.4% and 58.6%. Since the 97.5% confidence interval (stratum adjusted Mantel-Haenszel test) of the difference in CR_{0-24h} 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 ($AUC_{0-\infty}$) were dose proportional over the dose range of 3.0 to 80 $\mu\text{g}/\text{kg}$ 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 \pm SD) and time to maximum concentration (T_{max}) 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 T_{max} 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, Aloxi 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 5HT₃ 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 [¹⁴C]-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 ($t_{1/2}$) of palonosetron was 37 ± 12 hours (mean \pm SD), and in cancer patients, $t_{1/2}$ 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 \pm 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. Aloxi 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 from 10 µg/kg to 20 µg/kg a dose-proportional increase in mean AUC was observed. Following single dose intravenous infusion of Aloxi 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 Aloxi 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-∞} , 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 _{1/2} , 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_{1/2} 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 V_{ss} is reported for paediatric cancer patients, whereas V_z 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 Aloxi is intended for single application in humans, these findings are not considered relevant for clinical use.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:

Glycerol Monocaprylocaproate (type I)
Polyglycerol oleate
Glycerol
Purified water
Butylhydroxyanisole

Capsule shell:

Gelatin
Sorbitol
Glycerol
Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

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. MARKETING AUTHORISATION HOLDER

Helsinn Birex Pharmaceuticals Limited.
Damastown
Mulhuddart
Dublin 15
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/306/003

EU/1/04/306/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 March 2005

Date of latest renewal: 23 March 2010

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>

ANNEX II

- A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RETRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETNG AUTHORISATION**
- D. CONDITIONS OR RETRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Helsinn Birex Pharmaceuticals Ltd.
Damastown, Mulhuddart, Dublin 15
Ireland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Aloxi solution for injection: Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Aloxi soft capsules: Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Aloxi 250 micrograms solution for injection
Palonosetron (as hydrochloride)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml of solution contains 50 micrograms palonosetron (as hydrochloride).
Each vial of 5 ml of solution contains 250 micrograms palonosetron (as hydrochloride).

3. LIST OF EXCIPIENTS

Also contains mannitol, disodium edetate, sodium citrate, citric acid monohydrate, water for injections, sodium hydroxide and hydrochloric acid.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 x 5 ml vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Intravenous use
Single use only

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused solution should be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Helsinn Birex Pharmaceuticals Ltd.
Damastown
Mulhuddart
Dublin 15
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/306/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

<2D barcode carrying the unique identifier included>

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Aloxi 250 micrograms solution for injection
Palonosetron
IV use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 ml

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Aloxi 500 micrograms soft capsules
Palonosetron

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 500 micrograms palonosetron. (as hydrochloride).

3. LIST OF EXCIPIENTS

Also contains sorbitol. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

1 soft capsule.
5 soft capsules.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Helsinn Birex Pharmaceuticals Ltd.
Damastown
Mulhuddart
Dublin 15
Republic of Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/306/002
EU/1/04/306/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Aloxi 500 micrograms

17. UNIQUE IDENTIFIER – 2D BARCODE

<2D barcode carrying the unique identifier included>

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Aloxi 500 micrograms soft capsules
Palonosetron

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Helsinn

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Aloxi 250 micrograms solution for injection Palonosetron

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Aloxi is and what it is used for
2. What you need to know before you are given Aloxi
3. How you are given Aloxi
4. Possible side effects
5. How to store Aloxi
6. Contents of the pack and other information

1. What Aloxi is and what it is used for

Aloxi contains the active substance palonosetron. This belongs to a group of medicines called ‘serotonin (5HT₃) antagonists’.

Aloxi is used in adults, adolescents and children over one month of age to help stop you feeling or being sick (nausea and vomiting) when having cancer treatments called chemotherapy.

It works by blocking the action of a chemical called serotonin, which can cause you to feel sick or to vomit.

2. What you need to know before you are given Aloxi

Do not take Aloxi if:

- you are allergic to palonosetron or any of the other ingredients of this medicine (listed in section 6).

You will not be given Aloxi if any of the above apply to you. If you are not sure, talk to your doctor or nurse before you are given this medicine.

Warnings and precautions

Talk to your doctor or nurse before you are given Aloxi if:

- you have a blocked bowel or have had repeated constipation in the past
- you have had heart problems or heart problems run in your family, such as changes in your heart beat (‘QT prolongation’)
- you have an imbalance of certain minerals in your blood which has not been treated - such as potassium and magnesium.

If any of the above applies to you (or you are not sure), talk to your doctor or nurse before you are given Aloxi.

Other medicines and Aloxi

Tell your doctor or nurse if you are taking, have recently taken or might take any other medicines. In particular, tell them if you are taking the following medicines:

Medicines for depression or anxiety

Tell your doctor or nurse if you are taking any medicines for depression or anxiety, including:

- medicines called SSRIs ('selective serotonin reuptake inhibitors') – such as fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, escitalopram
- medicines called SNRIs ('serotonin noradrenaline reuptake inhibitors') – such as venlafaxine, duloxetine (can lead to the development of serotonin syndrome and should be used with caution).

Medicines that can affect your heart beat

Tell your doctor or nurse if you are taking any medicines that affect your heart beat – this is because they could cause a heart beat problem when taken with Aloxi. This includes:

- medicines for heart problems such as amiodarone, nicardipine, quinidine
- medicines for infections such as moxifloxacin, erythromycin
- medicines for serious mental health problems such as haloperidol, chlorpromazine, quetiapine, thioridazine
- a medicine for feeling or being sick (nausea and vomiting) called domperidone.

If any of the above applies to you (or you are not sure), talk to your doctor or nurse before taking Aloxi – this is because these medicines could cause a heart beat problem when taken with Aloxi.

Pregnancy

If you are pregnant or think you might be pregnant, your doctor will not give you Aloxi unless it is clearly necessary. This is because we do not know if Aloxi may harm the baby.

Ask your doctor or nurse for advice before being given this medicine if you are pregnant or think you might be.

Breast-feeding

It is not known if Aloxi is found in breast milk.

Ask your doctor or nurse for advice before being given this medicine if you are breast-feeding.

Driving and using machines

You may feel dizzy or tired after being given this medicine. If this happens, do not drive or use any tools or machines.

Aloxi contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium-free'.

3. How you are given Aloxi

Aloxi is normally given by a doctor or nurse.

- You will be given the medicine about 30 minutes before the start of chemotherapy.

Adults

- The recommended dose of Aloxi is 250 micrograms.
- It is given as an injection into a vein.

Children and young people (aged 1 month to 17 years)

- The doctor will work out the right dose based on bodyweight.
- The maximum dose is 1500 micrograms.

- Aloxi will be given as a drip (a slow infusion into a vein).

It is not recommended you are given Aloxi in the days following chemotherapy unless you are going to have another chemotherapy cycle.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. The following side effects may happen with this medicine:

Serious side effects

Tell your doctor straight away if you notice any of the following serious side effects:

- allergic reaction - the signs may include swelling of the lips, face, tongue or throat, having difficulty breathing or collapsing, an itchy, lumpy rash (hives). This is very rare: may affect up to 1 in 10,000 people.

Tell your doctor straight away if you notice any of the serious side effects listed above.

Other side effects

Tell your doctor if you notice any of the following side effects:

Adults

Common: may affect up to 1 in 10 people

- headache, feeling dizzy,
- constipation, diarrhoea.

Uncommon: may affect up to 1 in 100 people

- change in the colour of the vein and veins becoming larger
- feeling happier than usual or feeling anxious
- feeling sleepy or trouble sleeping
- decrease or loss of appetite
- weakness, feeling tired, fever or flu like symptoms
- numbness, burning, prickling or tingling sensations on the skin
- itchy skin rash
- impaired vision or eye irritation
- motion sickness
- ringing in the ear
- hiccups, passing wind (flatulence), dry mouth or indigestion
- abdominal (stomach) pain
- difficulty passing water (urinating)
- joint pain.

Tell your doctor if you notice any of the side effects listed above.

Uncommon side effects shown in tests: may affect up to 1 in 100 people

- high or low blood pressure
- abnormal heart rate or lack of blood flow to the heart
- abnormally high or low levels of potassium in the blood
- high levels of sugar in the blood or sugar in the urine
- low levels of calcium in the blood

- high levels of the pigment bilirubin in the blood
- high levels of certain liver enzymes
- ECG (electrocardiogram) abnormalities ('QT prolongation').

Very rare: may affect up to 1 in 10,000 people

- Burning, pain or redness at the injection site

Children and young people

Common: may affect up to 1 in 10 people

- headache.

Uncommon: may affect up to 1 in 100 people

- dizziness
- jerky body movements
- abnormal heart rate
- coughing or shortness of breath
- nosebleed
- itchy skin rash or hives
- fever
- pain at the site of infusion.

Tell your doctor if you notice any of the side effects listed above.

Reporting of side effects

If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Aloxi

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the vial and carton after 'EXP'. The expiry date refers to the last day of that month.
- This medicine does not require any special storage conditions.
- Single use only, any unused solution should be disposed of.

6. Contents of the pack and other information

What Aloxi contains

- The active substance is palonosetron (as hydrochloride). Each ml of solution contains 50 micrograms palonosetron. Each vial of 5 ml of solution contains 250 micrograms of palonosetron.
- The other ingredients are mannitol, disodium edetate, sodium citrate, citric acid monohydrate, water for injections, sodium hydroxide and hydrochloric acid.

What Aloxi looks like and contents of the pack

Aloxi solution for injection is a clear, colourless solution and is supplied in a pack of one Type I glass vial with chlorobutyl siliconised rubber stopper and aluminium cap, which contains 5 ml of the solution. Each vial contains one dose.

Available in packs of 1 vial containing 5 ml of solution.

Marketing Authorisation Holder and Manufacturer

Helsinn Birex Pharmaceuticals Ltd.,
Damastown,
Mulhuddart,
Dublin 15,
Ireland.

This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>

Package leaflet: Information for the patient

Aloxi 500 micrograms soft capsules Palonosetron

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Aloxi is and what it is used for
2. What you need to know before you take Aloxi
3. How to take Aloxi
4. Possible side effects
5. How to store Aloxi
6. Contents of the pack and other information

1. What Aloxi is and what it is used for

Aloxi contains the active substance palonosetron. This belongs to a group of medicines called ‘serotonin (5HT₃) antagonists’.

Aloxi is used in adults to help stop you feeling or being sick (nausea and vomiting) when having cancer treatments called chemotherapy.

It works by blocking the action of a chemical called serotonin, which can cause you to feel sick or to vomit.

2. What you need to know before you take Aloxi

Do not take Aloxi if:

- you are allergic to palonosetron or any of the other ingredients of this medicine (listed in section 6).

Do not take Aloxi if any of the above applies to you. If you are not sure, talk to your doctor or pharmacist before taking this medicine.

Warnings and precautions

Talk to your doctor or pharmacist before taking Aloxi if:

- you have a blocked bowel or have had repeated constipation in the past
- you have had heart problems or heart problems run in your family, such as changes in your heart beat (‘QT prolongation’)
- you have an imbalance of certain minerals in your blood which has not been treated - such as potassium and magnesium.

Children

Do not give this medicine to children

Other medicines and Aloxi

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. In particular, tell them if you are taking the following medicines:

Medicines for depression or anxiety

Tell your doctor or pharmacist if you are taking any medicines for depression or anxiety, including:

- medicines called SSRIs ('selective serotonin reuptake inhibitors') – such as fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, escitalopram
- medicines called SNRIs ('serotonin noradrenaline reuptake inhibitors') – such as venlafaxine, duloxetine (can lead to the development of serotonin syndrome and should be used with caution).

If any of the above applies to you (or you are not sure), talk to your doctor or pharmacist before taking Aloxi.

Medicines that can affect your heart beat

Tell your doctor or pharmacist if you are taking any medicines that affect your heart beat – this is because they could cause heart beat problems when taken with Aloxi. This includes:

- medicines for heart problems such as amiodarone, nicardipine, quinidine
- medicines for infections such as moxifloxacin, erythromycin
- medicines for serious mental health problems such as haloperidol, chlorpromazine, quetiapine, thioridazine
- a medicine for feeling or being sick (nausea and vomiting) called domperidone.

If any of the above applies to you (or you are not sure), talk to your doctor or pharmacist before taking Aloxi – this is because these medicines could cause heart beat problems when taken with Aloxi.

Pregnancy

If you are pregnant or think you might be pregnant, your doctor will not use Aloxi unless it is clearly necessary. This is because we do not know if Aloxi may harm the baby.

Ask your doctor or pharmacist for advice before using this medicine if you are pregnant or think you might be.

Breast-feeding

It is not known if Aloxi is found in breast milk.

Ask your doctor or pharmacist for advice before using this medicine if you are breast-feeding.

Driving and using machines

You may feel dizzy or tired after taking this medicine. If this happens, do not drive or use any tools or machines.

Aloxi contains sorbitol and may contain traces of soya

This medicine contains 7 mg sorbitol (a type of sugar) in each capsule. If you have been told by your doctor that you have an intolerance to some sugars, talk to your doctor before taking this medicine.

Aloxi may contain traces of lecithin which comes from soya. If you are allergic to peanut or soya, do not take this medicine. See your doctor straight away if you notice any signs of an allergic reaction. The signs may include hives, skin rash, itching, difficulty breathing or swallowing, swollen mouth, face, lips, tongue or throat and sometimes a drop in blood pressure.

3. How to take Aloxi

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

- The recommended dose is one capsule (500 micrograms).
- You will normally take the capsule about 60 minutes before the start of your chemotherapy.
- This medicine can be taken with or without food.

It is not recommended to take Aloxi in the days following chemotherapy unless you are going to have another chemotherapy cycle.

If you take more Aloxi than you should

If you think you may have taken more than you should, tell your doctor straight away.

If you forget to take Aloxi

It is unlikely that you will forget to take this medicine. However, if you think you have forgotten to take your dose, tell your doctor straight away.

If you stop taking Aloxi

Do not stop taking this medicine without talking to your doctor. If you decide not to take Aloxi (or other similar medicines), it is likely your chemotherapy will cause you to feel sick or be sick (nausea and vomiting).

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. The following side effects may happen with this medicine:

Serious side effects

Tell your doctor straight away if you notice any of the following serious side effects:

- allergic reaction - the signs may include swelling of the lips, face, tongue or throat, having difficulty breathing or collapsing, an itchy, lumpy rash (hives). This is very rare: may affect up to 1 in 10,000 people.

Tell your doctor straight away if you notice any of the serious side effects listed above.

Other side effects

Tell your doctor if you notice any of the following side effects:

Common: may affect up to 1 in 10 people

- headache.

Uncommon: may affect up to 1 in 100 people

- trouble sleeping
- shortness of breath
- eye swelling
- abnormal electrical impulses in the heart
- constipation
- feeling sick (nausea)
- high levels of the pigment 'bilirubin' (a marker of liver problems) in the blood
- muscle pain.

Tell your doctor if you notice any of the side effects listed above.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via **the national reporting system** listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Aloxi

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the blister and carton after “EXP”. The expiry date refers to the last day of that month.
- This medicine does not require any special storage conditions.

6. Contents of the pack and other information

What Aloxi contains

- The active substance is palonosetron. Each capsule contains 500 micrograms palonosetron (as hydrochloride).
- The other ingredients are glycerol monocaprylocaproate (type I), polyglycerol oleate, glycerol, purified water, butylhydroxyanisole, gelatin, sorbitol, titanium dioxide.

What Aloxi looks like and contents of the pack

Aloxi 500 micrograms soft capsules are plain, light beige, opaque, round to oval soft capsules, filled with a clear yellowish solution. They are supplied in polyamide/aluminium/PVC blisters containing one or five capsules.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Helsinn Birex Pharmaceuticals Ltd.,
Damastown,
Mulhuddart,
Dublin 15,
Ireland.

This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency website:
<http://www.ema.europa.eu>