Aloxi PONV summary of product characteristics (SmPC)

1. Name of the medicinal product
Aloxi PONV 0.075 mg /1.5 mL sterile solution

1.1 Product name
Aloxi PONV

1.2 Strength
0.075 mg / 1.5 mL (concentration: 0.05 mg/mL)

1.3 Pharmaceutical dosage form
ALOXI PONV is a sterile solution for injection single-use

2.Qualitative and quantitative declaration
1 ml contain Palonosetron (as hydrochloride) 0.05 mg

3. Pharmaceutical form
clear, colorless sterile solution

4. Clinical particulars
4.1 Therapeutic indication
Postoperative Nausea and Vomiting in Adults
ALOXI PONV is indicated for prevention of postoperative nausea and vomiting (PONV) for up to 24 hours following surgery. Efficacy beyond 24 hours has not been demonstrated.
As with other antiemetics, routine prophylaxis is not recommended in patients in whom there is little expectation that nausea and/or vomiting will occur postoperatively. In patients where nausea and vomiting must be avoided during the postoperative period, ALOXI PONV is recommended even where the incidence of postoperative nausea and/or vomiting is low.

4.2 Posology and method of administration
Recommended Dosing
Postoperative Nausea and Vomiting
Dosage for Adults - a single 0.075 mg intravenous dose administered over 10 seconds immediately before the induction of anesthesia.

Elderly people : No dose adjustment is necessary for the elderly.

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.

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

4.3 Contraindication
ALOXI PONV is contraindicated in patients known to have hypersensitivity to the drug or any of its components.

4.4 Special warning and precautions for use

1. Hypersensitivity

Hypersensitivity reactions, including anaphylaxis, have been reported with or without known hypersensitivity to other 5-HT3 receptor antagonists.

2 Serotonin Syndrome

The development of serotonin syndrome has been reported with 5-HT3 receptor antagonists. Most reports have been associated with concomitant use of serotonergic drugs (e.g., selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors, mirtazapine, fentanyl, lithium, tramadol, and intravenous methylene blue). Some of the reported cases were fatal. Serotonin syndrome occurring with overdose of another 5-HT3 receptor antagonist alone has also been reported. The majority of reports of serotonin syndrome related to 5-HT3 receptor antagonist use occurred in a postanesthesia care unit or an infusion center. Symptoms associated with serotonin syndrome may include the following combination of signs and symptoms: mental status changes (e.g. agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, with or without gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Patients should be monitored for the emergence of serotonin syndrome, especially with concomitant use of Aloxi PONV and other serotonergic drugs. If symptoms of serotonin syndrome occur, discontinue Aloxi PONV and initiate supportive treatment. Patients should be informed of the increased risk of serotonin syndrome, especially if Aloxi PONV is used concomitantly with other serotonergic drugs

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

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

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

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

Lactation
It is not known whether ALOXI PONV is present in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants and the potential for tumorigenicity shown for palonosetron in the rat carcinogenicity .
a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

4.7 Effects on ability to drive and use machine
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
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The adverse reactions cited in Table 1 were reported in ≥ 2% of adults receiving I.V. Aloxi PONV 0.075 mg immediately before induction of anesthesia in one phase 2 and two phase 3 randomized placebo-controlled trials. Rates of events between palonosetron and placebo groups were similar. Some events are known to be associated with, or may be exacerbated by concomitant perioperative and intraoperative medications administered in this surgical population. Please refer to Section 11.2, thorough QT/QTc study results, for data demonstrating the lack of palonosetron effect on QT/QTc.

Table 1: Adverse Reactions from Postoperative Nausea and Vomiting
Studies ≥ 2% in any Treatment Group

Event	Aloxi PONV 0.075 mg (N=336)	Placebo (N=369)
Electrocardiogram QT prolongation	16 (5 %)	11 (3%)
Bradycardia	13 (4 %)	16 (4%)
Headache	11 (3 %)	14 (4%)
Constipation	8 (2 %)	11 (3%)

In these clinical trials, the following infrequently reported adverse reactions, assessed by investigators as treatment-related or causality unknown, occurred following administration of ALOXI PONV to adult patients receiving concomitant perioperative and intraoperative medications including those associated with anesthesia:

Cardiovascular: 1%: electrocardiogram QTc prolongation, sinus bradycardia, tachycardia, < 1%: blood pressure decreased, hypotension, hypertension, arrhythmia, ventricular extra systoles, generalized edema, ECG T wave amplitude decreased, platelet count decreased. The frequency of these adverse effects did not appear to be different from placebo.

Dermatological: 1%: pruritus.

Gastrointestinal System: 1%: flatulence, < 1%: dry mouth, upper abdominal pain, salivary hypersecretion, dyspepsia, diarrhea, intestinal hypomotility, anorexia.

General: < 1%: chills.

Liver: 1%: increases in AST and/or ALT, < 1%: hepatic enzyme increased.

Metabolic: < 1%: hypokalemia, anorexia.

Nervous System: < 1%: dizziness.

Respiratory: < 1%: hypoventilation, laryngospasm.

Urinary System: 1%: urinary retention.

Post marketing Experience:
The following adverse reactions have been identified during post approval use of ALOXI PONV. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

4.9 Overdose
There is no known antidote to ALOXI PONV. Overdose should be managed with supportive care.

5. Pharmacological properties

Pharmacotherapeutic group: Antiemetics and anti nauseants, serotonin (5HT3) antagonists. ATC code: A04AA05
Palonosetron is a selective high-affinity receptor antagonist of the 5HT3 receptor.

Postoperative nausea and vomiting is influenced by multiple patient, surgical and anesthesia related factors and is triggered by release of 5-HT in a cascade of neuronal events involving both the central nervous system and the gastrointestinal tract. The 5-HT3 receptor has been demonstrated to selectively participate in the emetic response.

5.1 Pharmacodynamic properties
The effect of palonosetron on blood pressure, heart rate, and ECG parameters including QTc were comparable to ondansetron and dolasetron in CINV clinical trials. In PONV clinical trials the effect of palonosetron on the QTc interval was no different from placebo. In non-clinical studies palonosetron possesses the ability to block ion channels involved in ventricular de- and re-polarization and to prolong action potential duration.

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

5.2 Pharmacokinetic properties
After intravenous dosing of palonosetron in healthy subjects and cancer patients, an initial decline in plasma concentrations is followed by a slow elimination from the body. Mean maximum plasma concentration (Cmax) and area under the concentration-time curve (AUC0-∞) are generally doseproportional over the dose range of 0.3–90 mcg/kg in healthy subjects and in cancer patients. Following single I.V. dose of palonosetron at 3 mcg/kg (or 0.21 mg/70 kg) to six cancer patients, mean (±SD) maximum plasma concentration was estimated to be 5630 ± 5480 ng/L and mean AUC was 35.8 ± 20.9 h•mcg/L.

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

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

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

<u>Metabolism</u>
Palonosetron is eliminated by multiple routes with approximately 50% metabolized to form two primary metabolites: N-oxide-palonosetron and 6-Shydroxy-palonosetron. These metabolites each

have less than 1% of the 5- HT3 receptor antagonist activity of palonosetron. In vitro metabolism studies have suggested that CYP2D6 and to a lesser extent, CYP3A4 and CYP1A2 are involved in the metabolism of palonosetron. However, clinical pharmacokinetic parameters are not significantly different between poor and extensive metabolizers of CYP2D6 substrates.

Elimination

After a single intravenous dose of 10 mcg/kg [14C]-palonosetron, approximately 80% of the dose was recovered within 144 hours in the urine with palonosetron representing approximately 40% of the administered dose. In healthy subjects, the total body clearance of palonosetron was 0.160 ± 0.035 L/h/kg and renal clearance was 0.067± 0.018 L/h/kg. Mean terminal elimination half-life is approximately 40 hours.

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.

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.

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 from10 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 (CT) reported at the end of the 15 minute infusion were highly variable in all age groups and tended to be lower in patients < 6 years than in older 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
$AUC_{0-\infty}$, 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 T½which 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.

5.3 Preclinical safety data

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 104-week carcinogenicity study in CD-1 mice, animals were treated with oral doses of palonosetron at 10, 30 and 60 mg/kg/day. Treatment with palonosetron was not tumorigenic. The highest tested dose produced a systemic exposure to palonosetron (Plasma AUC) of about 150 to 289 times the human exposure (AUC= 29.8 h•mcg/L) at the recommended intravenous dose of 0.25 mg. In a 104-week carcinogenicity study in Sprague-Dawley rats, male and female rats were treated with oral doses of 15, 30 and 60 mg/kg/day and 15, 45 and 90 mg/kg/day, respectively. The highest doses produced a systemic exposure to palonosetron (Plasma AUC) of 137 and 308 times the human exposure at the recommended dose. Treatment with palonosetron produced increased incidences of adrenal benign pheochromocytoma and combined benign and malignant pheochromocytoma, increased incidences of pancreatic Islet cell adenoma and combined adenoma and carcinoma and pituitary adenoma in male rats. In female rats, it produced hepatocellular adenoma and carcinoma and increased the incidences of thyroid C-cell adenoma and combined adenoma and carcinoma.

Palonosetron was not genotoxic in the Ames test, the Chinese hamster ovarian cell (CHO/HGPRT) forward mutation test, the ex vivo hepatocyte unscheduled DNA synthesis (UDS) test or the mouse micronucleus test. It was, however, positive for clastogenic effects in the Chinese hamster ovarian (CHO) cell chromosomal aberration test. Palonosetron at oral doses up to 60 mg/kg/day (about 1894 times the recommended human intravenous dose based on body surface area) was found to have no effect on fertility and reproductive performance of male and female rats.

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.

6.4 Special precautions for storage
Store at or below 30°C Excursions permitted to 15–30°C (59- 86°F).
Protect from freezing.
Protect from light.

6.5 Nature and contents of container
Type I glass vial with rubber stopper and aluminium cap.
Available in packs of 1 vial 3 ml containing 1.5 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. MANUFACTURED BY
FAREVA PAU
Fareva Pau 1, Avenue du Bearn, IDRON 64320,France

Marketing authorization holder

DKSH (Thailand) Limited

Bangkok , Thailand

8. Marketing authorization numbers

Xxxxxxx

9. Date of first authorization/renewal of the authorization

xxxxxxx

10. Date of revision of the text

7 Dec 2021