SINGAPORE PRODUCT INFORMATION

PALONOSETRON - AFT

Solution for injection

1 PRODUCT NAME

PALONOSETRON-AFT SOLUTION FOR INJECTION 0.25MG/5ML

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 mL vial contains 0.28 mg of palonosetron hydrochloride equivalent to 0.25 mg of palonosetron.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Palonosetron - AFT is supplied as a sterile, clear, colorless, non-pyrogenic, isotonic, buffered solution for intravenous administration. The pH of the injection is 4.5 – 5.5 and the osmotic pressure is 265 mOsmol/kg to 315 mOsmol/kg.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Chemotherapy-induced nausea and vomiting in adults

Palonosetron – AFT is indicated for:

- Moderately emetogenic cancer chemotherapy – prevention of acute and delayed nausea and vomiting associated with initial and repeat courses
- Highly emetogenic cancer chemotherapy – prevention of acute nausea and vomiting associated with initial and repeat courses

Chemotherapy-induced nausea and vomiting in paediatric patients aged 1 month to less than 17 years

Palonosetron – AFT is indicated for:

- Prevention of acute nausea and vomiting associated with initial and repeat courses of moderately or highly emetogenic cancer chemotherapy

Postoperative nausea or vomiting in adults

Palonosetron – AFT is indicated for:

- Prevention of postoperative nausea and vomiting (PONV) for up to 24 hours following surgery. Efficacy beyond 24 hours has not been demonstrated.

As with other antiemetics, routine prophylaxis is not recommended in patients in whom there is little expectation that nausea and-or vomiting will occur postoperatively. In patients where nausea and vomiting must be avoided during the postoperative period,

Palonosetron – AFT is recommended even where the incidence of postoperative nausea and/ or vomiting is low.

4.2 DOSE AND METHOD OF ADMINISTRATION

Recommended dosing

Chemotherapy-induced nausea and vomiting

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

* Note different dosing units in paediatrics

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

Postoperative nausea and vomiting

Dosage for adults – a single dose of 0.075 mg I.V. dose administered over 10 seconds immediately before the induction of anaesthesia.

Instructions for IV administration

Palonosetron-AFT is supplied ready for intravenous injection at a concentration of 0.05mg/ml (50mcg/ml).

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

Flush the infusion line with normal saline before and after administration of Palonosetron – AFT.

Contains no antimicrobial agent. Palonosetron – AFT is for single use in one patient only. Discard any residue.

4.3 CONTRAINDICATIONS

Palonosetron – AFT is contraindicated in patients with known hypersensitivity to the drug or to any of its components.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

Hypersensitivity reactions may occur in patients who have exhibited hypersensitivity to other selective 5-HT3 receptor antagonists. ALOXI should not be used to prevent or treat nausea and vomiting in the days following chemotherapy if not associated with another chemotherapy administration.

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 post- anesthesia care unit or an infusion center.

Symptoms associated with serotonin syndrome may include the following combination of signs and symptoms: mental status changes (e.g. agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g.tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, with or without gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Patients should be monitored for the emergence of serotonin syndrome, especially with concomitant use of Palonosetron-AFT and other serotonergic drugs. If symptoms of serotonin syndrome occur, discontinue Palonosetron-AFT and initiate supportive treatment. Patients should be informed of the increased risk of serotonin syndrome, especially if Palonosetron-AFT is used concomitantly with other serotonergic drugs.

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.

Cardiac conduction

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 – Pharmacodynamic properties). However, as for the other 5-HT3 antagonists, caution should be exercised in the concomitant use of palonosetron with medicinal products that increase the QT interval or in patients who have or are likely to develop prolongation of the QT interval.

Race

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

Use in hepatic impairment

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

Use in renal impairment

Mild to moderate renal impairment does not significantly affect palonosetron pharmacokinetic parameters. Total systemic exposure increased by approximately 28%

in severe renal impairment relative to healthy subjects. Dosage adjustment is not necessary in patients with any degree of renal impairment.

Use in the elderly

Population pharmacokinetic analysis and clinical safety and efficacy data did not reveal any differences between cancer patients ≥ 65 years of age and younger patients (18 to 64 years). No dose adjustment is required for these patients.

Effects on laboratory tests

No data available

4.5 INTERACTIONS WITH OTHER MEDICINES 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, CPY2D6, 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 during 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) [see Warnings and Precautions]

A study in healthy volunteers involving the co-administration of single IV doses of palonosetron (250 microgram) and dexamethasone (20 mg) demonstrated no significant interaction.

In a study in healthy volunteers involving the co-administration of a single dose of IV palonosetron (250 microgram) on Day 1 with single doses of aprepitant (125 mg/ 80 mg/ 80 mg) on Days 1, 2 and 3, the pharmacokinetics of palonosetron were not significantly altered (C_{max}: 15% increase, AUC: no change).

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

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

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Pregnancy

Teratogenic Effects: Category B

Teratology studies have been performed in rats at oral doses up to 60 mg/kg/day (1894 times the recommended human intravenous dose based on body surface area) and rabbits at oral doses up to 60 mg/kg/day (3789 times the recommended human intravenous dose based on body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to palonosetron. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, palonosetron should be used during pregnancy only if clearly needed.

Labor and Delivery

Since the effect of palonosetron is unknown on mother or child, it should not be administered to patients during labor or delivery.

Nursing Mothers

It is not known whether palonosetron is excreted in human milk. Because many drigs 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 rat carcinogenicity study, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

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 ADVERSE EFFECTS (UNDESIREABLE EFFECTS)

Chemotherapy-Induced Nausea and Vomiting (CINV) in Adults

In clinical trials for the prevention of nausea and vomiting induced by moderately or highly emetogenic chemotherapy, 1374 adult patients received palonosetron. Adverse reactions were similar in frequency and severity with palonosetron and ondansetron or dolasetron. Following is a listing of all adverse reactions reported by ≥ 2% of patients in these trials (Table 1).

Table 1: Adverse reactions from chemotherapy-induced nausea and vomiting studies, ≥ 2% in any treatment group

Event	Palonosetron 250 microgram (N=633)	Ondansetron 32 mg IV (N=410)	Dolasetron 100 mg IV (N=194)
Headache	60 (9%)	34 (8%)	32 (16%)
Constipation	29 (5%)	8 (2%)	12 (6%)
Diarrhoea	8 (1%)	7 (2%)	4 (2%)
Dizziness	8 (1%)	9 (2%)	4 (2%)

Fatigue	3 (< 1%)	4 (1%)	4 (2%)
Abdominal pain	1 (< 1%)	2 (< 1%)	3 (2%)
Insomnia	1 (< 1%)	3 (1%)	3 (2%)

In other studies, 2 subjects experienced severe constipation following a single palonosetron dose of approximately 0.75 mg, three times the recommended dose. One patient received a 10 µg/kg oral dose in a post-operative nausea and vomiting study and one healthy subject received a 0.75 mg IV dose in a pharmacokinetic study.

In clinical trials, the following infrequently reported adverse reactions, assessed by investigators as treatment-related or causality unknown, occurred following administration of palonosetron to adult patients receiving concomitant cancer chemotherapy:

Cardiovascular: 1%: non-sustained tachycardia, bradycardia, hypotension, < 1%: hypertension, myocardial ischemia, extrasystoles, sinus tachycardia, sinus arrhythmia, supraventricular extrasystoles and QT prolongation. In many cases, the relationship to ALOXI was unclear.

Dermatological: < 1%: allergic dermatitis, pruritic rash.

Hearing and Vision: < 1%: motion sickness, tinnitus, eye irritation and amblyopia.

Gastrointestinal system: 1%: diarrhoea, < 1%: dyspepsia, upper abdominal pain, dry mouth, hiccups and flatulence.

General: 1%: weakness, asthenia < 1%: fatigue, fever, hot flash, flu-like syndrome.

Liver: < 1%: transient, asymptomatic increases in AST and/or ALT and bilirubin. These changes occurred predominantly in patients receiving highly emetogenic chemotherapy.

Metabolic: 1%: hyperkalaemia, < 1%: electrolyte fluctuations, hypocalcaemia, hyperglycaemia, metabolic acidosis, glycosuria, appetite decrease, anorexia.

Musculoskeletal: < 1%: arthralgia.

Nervous System: 1%: dizziness, < 1%: somnolence, insomnia, hypersomnia, paresthesia, and peripheral sensory neuropathy.

Psychiatric: 1%: anxiety, < 1%: euphoric mood.

Urinary System: < 1%: urinary retention.

Vascular: < 1%: vein discoloration, vein distention.

Chemotherapy-Induced Nausea and Vomiting (CINV) in Paediatrics

In a pediatric clinical trial for the prevention of chemotherapy-induced nausea and vomiting, 163 cancer patients received a single 20 µg/kg (maximum 1.5 mg) intravenous infusion of palonosetron 30 minutes before beginning the first cycle of emetogenic chemotherapy. Patients had a mean age of 8.4 years (range 2 months to 16.9 years) and were 46% male; and 93% white.

The following adverse effects were reported for palonosetron:

Nervous system: <1%: headache, dizziness, dyskinesia.

General: <1%: infusion site pain.

Dermatological: <1%: allergic dermatitis, skin disorder.

In the trial, adverse reactions were evaluated in paediatric patients receiving palonosetron for up to 4 chemotherapy cycles.

Post-Operative Nausea and Vomiting (PONV) in Adults

The adverse reactions cited in Table 2 were reported in ≥ 2% of adults receiving I.V. palonosetron 75 microgram immediately before induction of anaesthesia in one phase 2 and two phase 3 randomised 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.

Table 2: Adverse reactions from postoperative nausea and vomiting studies ≥ 2% in 75 µg or placebo treatment groups

Event	Palonosetron 75 microgram (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 to adult patients receiving concomitant perioperative and intraoperative medications including those associated with anaesthesia:

Cardiovascular: 1%: electrocardiogram QTc prolongation, sinus bradycardia, tachycardia, < 1%: blood pressure decreased, hypotension, hypertension, arrhythmia, ventricular extrasystoles, generalised oedema, 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, diarrhoea, intestinal hypomotility, anorexia.

General: < 1%: chills.

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

Metabolic: < 1%: hypokalaemia, anorexia.

Nervous System: < 1%: dizziness.

Respiratory: < 1%: hypoventilation, laryngospasm.

Urinary System: 1%: urinary retention.

Post-marketing experience

In post-marketing reports there have been very rare cases of:

- Hypersensitivity reactions including anaphylaxis and shock, and
- Injection site reactions such as burning, induration, discomfort and pain

4.9 OVERDOSE

There is no known antidote to palonosetron. Overdose should be managed with supportive care. Fifty adult cancer patients were administered palonosetron at a dose of 90 microgram/kg (equivalent to 6 mg fixed dose) as part of a dose ranging study. This is approximately 25 times the recommended dose of 250 microgram. This dose group had a similar incidence of adverse events compared to the other dose groups and no dose response effects were observed. Dialysis studies have not been performed; however, due to the large volume of distribution, dialysis is unlikely to be an effective treatment for palonosetron overdose. A single intravenous dose of palonosetron at 30 mg/kg (947 and 474 times the human dose for rats and mice, respectively, based on body surface area) was lethal to rats and mice. The major signs of toxicity were convulsions, gasping, pallor, cyanosis and collapse.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Palonosetron hydrochloride is an antiemetic and antinauseant agent. It is a selective serotonin subtype 3 (5-HT3) receptor antagonist with a strong binding affinity for this receptor.

Cancer chemotherapy may be associated with a high incidence of nausea and vomiting, particularly when certain agents, such as cisplatin, are used. 5-HT3 receptors are located on the nerve terminals of the vagus in the periphery and centrally in the chemoreceptor trigger zone of the area postrema. It is thought that chemotherapeutic agents produce nausea and vomiting by releasing serotonin from the enterochromaffin cells of the small intestine and that the released serotonin then activates 5-HT3 receptors located on vagal afferents to initiate the vomiting reflex.

Pharmacodynamics

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

Clinical trials

Chemotherapy-Induced Nausea and Vomiting (CINV) in adults

Single-dose palonosetron administration

Efficacy of single-dose palonosetron injection in preventing nausea and vomiting induced by moderately and highly emetogenic chemotherapy was studied in a phase 2 dose-ranging trial and three phase 3 trials. In the phase 3 trials, the primary efficacy endpoint was complete response rate (no emetic episodes and no rescue medication). Prevention of nausea was assessed as a secondary efficacy endpoint. The safety and efficacy of palonosetron in repeated courses of chemotherapy was also studied.

Moderately emetogenic chemotherapy

Two Phase 3, double-blind trials involving 1132 patients compared single-dose IV palonosetron with either single-dose IV ondansetron (study 1) or dolasetron (study 2) given 30 minutes prior to moderately emetogenic chemotherapy including carboplatin, cisplatin ≤ 50 mg/m^2, cyclophosphamide < 1500 mg/m^2, doxorubicin > 25 mg/m^2, epirubicin, irinotecan, and methotrexate > 250 mg/m^2. Concomitant corticosteroids were not administered prophylactically in study 1 and were only used by 4-6% of patients in study 2. The majority of patients in these studies were women (77%), White (65%) and naïve to previous chemotherapy (54%). The mean age was 55 years, (age range 18-97).

Highly emetogenic chemotherapy

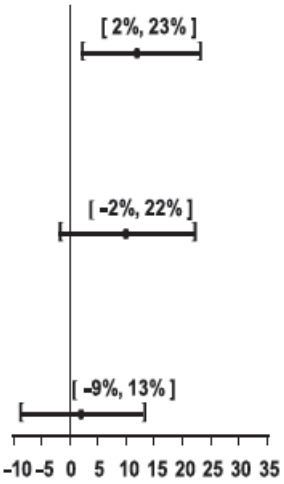
A Phase 2, double-blind, dose-ranging study evaluated the efficacy of single-dose IV palonosetron from 0.3 to 90 µg/kg (equivalent to < 0.1 mg to 6 mg fixed dose) in 161 chemotherapy-naïve adult cancer patients receiving highly-emetogenic chemotherapy (either cisplatin ≥ 70 mg/m^2 or cyclophosphamide > 1100 mg/m^2). Concomitant corticosteroids were not administered prophylactically. Analysis of data from this trial indicates that 250 microgram is the lowest effective dose in preventing acute nausea and vomiting induced by highly emetogenic chemotherapy.

A Phase 3, double-blind trial involving 667 patients compared single-dose IV palonosetron with single-dose IV ondansetron (study 3) given 30 minutes prior to highly emetogenic chemotherapy including cisplatin ≥ 60 mg/m^2, cyclophosphamide > 1500 mg/m^2, and dacarbazine. Corticosteroids were co-administered prophylactically before chemotherapy in 67% of patients. Of the 667 patients, 51% were women, 60% White, and 59% naïve to previous chemotherapy. The mean age was 52 years.

Efficacy results

The antiemetic activity of palonosetron HCl was evaluated during the acute phase (0-24 hours) (Table 3), delayed phase (24-120 hours) (Table 4), and overall phase (0-120 hours) (Table 5) post-chemotherapy in Phase 3 trials.

Table 3: Prevention of acute nausea and vomiting (0-24 hours): Complete response rates

Chemotherapy	Study	Treatment group	N [a]	% with complete response	p-value [b]	97.5% confidence interval Palonosteron minus comparator [c]
Moderately Emetogenic	1	Palonosetron 0.25 mg	189	81	0.009	
		Ondansetron 32 mg I.V.	185	69		
	2	Palonosetron 0.25 mg	189	63	NS	
		Dolasetron 100 mg I.V.	191	53		
Highly Emetogenic	3	Palonosetron 0.25 mg	223	59	NS	
		Ondansetron 32 mg I.V.	221	57		

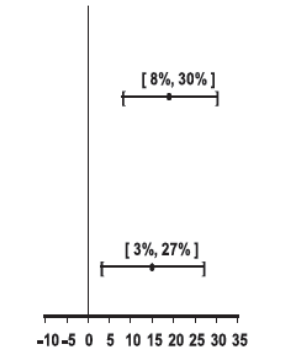
a Intent-to-treat cohort

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

c These studies were designed to show non-inferiority. A lower bound greater than -15% demonstrates non-inferiority between palonosetron and comparator.

These studies show that palonosetron HCl was effective in the prevention of acute nausea and vomiting associated with initial and repeat courses of moderately and highly emetogenic cancer chemotherapy. In study 3, efficacy was greater when prophylactic corticosteroids were administered concomitantly. Clinical superiority over other 5-HT3 receptor antagonists has not been adequately demonstrated in the acute phase.

Table 4: Prevention of delayed nausea and vomiting (24-120 hours): complete response rates

Chemotherapy	Study	Treatment group	N [a]	% with complete response	p-value [b]	97.5% confidence interval Palonosteron minus comparator [c]
Moderately Emetogenic	1	Palonosetron 0.25 mg	189	74	<0.001	
		Ondansetron 32 mg I.V.	185	55		
	2	Palonosetron 0.25 mg	189	54	0.004	
		Dolasetron 100 mg I.V.	191	39		

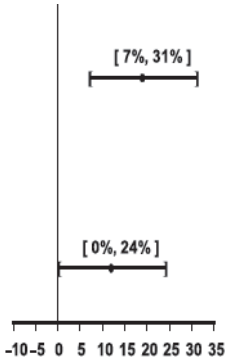
a Intent-to-treat cohort

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

c These studies were designed to show non-inferiority. A lower bound greater than -15% demonstrates non-inferiority between palonosetron and comparator.

These studies show that palonosetron HCl was effective in the prevention of delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic chemotherapy.

Table 5: Prevention of overall nausea and vomiting (0-120 hours): complete response rates

Chemotherapy	Study	Treatment group	N [a]	% with complete response	p-value [b]	97.5% confidence interval Palonosteron minus comparator [c]
Moderately Emetogenic	1	Palonosetron 0.25 mg	189	69	<0.001	
		Ondansetron 32 mg I.V.	185	50		
	2	Palonosetron 0.25 mg	189	46	0.021	
		Dolasetron 100 mg I.V.	191	34		

a Intent-to-treat cohort

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

c These studies were designed to show non-inferiority. A lower bound greater than -15% demonstrates non-inferiority between palonosetron and comparator.

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

Chemotherapy-induced nausea and vomiting in paediatrics

One double-blind, active-controlled clinical trial was conducted in pediatric cancer patients. The total population (N = 327) had a mean age of 8.3 years (range 2 months to 16.9 years) and were 53% male; and 96% white. Patients were randomized and received a 20 mcg/kg (maximum 1.5 mg) intravenous infusion of palonosetron HCl 30 minutes prior to the start of emetogenic chemotherapy (followed by placebo infusions 4 and 8 hours after the dose of palonosetron) or 150 mcg/kg of intravenous ondansetron 30 minutes prior to the start of emetogenic chemotherapy (followed by ondansetron 0.15 mg/kg infusions 4 and 8 hours after the first dose of ondansetron, with a maximum total dose of 32 mg). Emetogenic chemotherapies administered included doxorubicin, cyclophosphamide (<1500 mg/m^2), ifosfamide, cisplatin, dactinomycin, carboplatin, and daunorubicin. Adjuvant corticosteroids, including dexamethasone, were administered with chemotherapy in 55% of patients.

Complete Response in the acute phase of the first cycle of chemotherapy was defined as no vomiting, no retching, and no rescue medication in the first 24 hours after starting

chemotherapy. Efficacy was based on demonstrating non-inferiority of intravenous palonosetron compared to intravenous ondansetron. Non-inferiority criteria were met if the lower bound of the 97.5% confidence interval for the difference in Complete Response rates of intravenous palonosetron minus intravenous ondansetron was larger than -15%. The non-inferiority margin was 15%.

Efficacy Results

As shown in Table 6, intravenous palonosetron 20 mcg/kg (maximum 1.5 mg) demonstrated non-inferiority to the active comparator during 0 to 24 hour time interval.

Table 6: Prevention of acute nausea and vomiting (0-24 hours): complete response rates

I.V. Palonosetron 20 mcg/kg (N=165)	**I.V. Ondansetron 0.15 mg/kg × 3 (N=162)**	**Difference (97.5% confidence interval)*: I.V. Palonosetron minus I.V. ondansetron comparator**
59.4%	58.6%	0.36% (-11.7%, 12.4%)

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

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

Post-Operative Nausea and Vomiting (PONV) in adults

In one multicentre, randomised, stratified, double-blind, parallel-group, phase 3 clinical study (PALO-04-06), palonosetron was compared with placebo for the prevention of PONV in 546 patients undergoing abdominal and gynaecological surgery. All patients received general anaesthesia. PALO-04-06 was a pivotal study conducted predominantly in the US in the out-patient setting for patients undergoing elective gynaecologic or abdominal laparoscopic surgery and stratified at randomisation for the following risk factors: gender, non-smoking status, history of post-operative nausea and vomiting and/or motion sickness.

In PALO-04-06 patients were randomised to receive palonosetron 25, 50 or 75 microgram or placebo, each given intravenously immediately prior to induction of anaesthesia. The antiemetic activity of palonosetron was evaluated during the 0 to 72 hour time period after surgery.

Of the 138 patients treated with 75 microgram palonosetron in PALO-04-06 and evaluated for efficacy, 96% were women; 66% had a history of PONV or motion sickness; 85% were non-smokers. As for race, 63% were White, 20% were Black, 15% were Hispanic, and 1% were Asian. The age of patients ranged from 21 to 74 years, with a mean age of 37.9 years. Three patients were greater than 65 years of age.

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

Secondary efficacy endpoints included:

- Complete Response (CR) 0-48 and 0-72 hours

- Complete Control (CC) defined as CR and no more than mild nausea
- Severity of nausea (none, mild, moderate, severe)

The primary hypothesis in PALO-04-06 was that at least one of the three palonosetron doses was superior to placebo.

Results for complete response in PALO-04-06 for 75 microgram palonosetron versus placebo are described in the following table.

Table 7: Prevention of postoperative nausea and vomiting: Complete response (CR), PALO-04-06, Palonosetron 75 microgram Vs placebo

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

* To reach statistical significance for each co-primary endpoint, the required significance limit for the lowest p-value was p<0.017. Δ Difference (%): palonosetron 75 microgram minus placebo

Palonosetron 75 microgram reduced the severity of nausea compared to placebo. Analyses of other secondary endpoints indicate that palonosetron 75 microgram was numerically better than placebo, however, statistical significance was not formally demonstrated.

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 (C_{max}) and area under the concentration-time curve ($AUC_{0-\infty}$) are generally dose-proportional over the dose range of 0.3–90 µg/kg in healthy subjects and in cancer patients. Following single IV dose of palonosetron at 3 µg/kg (or 0.21 mg/70 kg) to six cancer patients, mean (±SD) maximum plasma concentration was estimated to be 5.6 ± 5.5 ng/mL and mean AUC was 35.8 ± 20.9 ng•hr/mL.

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 the initial phase of the plasma concentration-time curve (AUC 0-2.5hr) from Day 1 to Day 5 was 42 ± 34 %; how this finding relates to more conventional measures of systemic exposure is not known.

After intravenous administration of palonosetron 0.25 mg once daily for 3 days in 12 healthy subjects, the mean (± SD) increase in systemic exposure over 24 hours (AUC 0-24hr) from Day 1 to Day 3 was 110 ± 45 %.

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

Distribution

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

Metabolism

Palonosetron is eliminated by multiple routes with approximately 50% metabolized to form two primary metabolites: N-oxide-palonosetron and 6-S-hydroxy-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, CYP3A 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.

Excretion

After a single intravenous dose of 10 µg/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 160 ± 35 mL/h/kg and renal clearance was 66.5 ± 18.2 mL/h/kg. Mean terminal elimination half-life is approximately 40 hours.

Paediatric patients

Single-dose I.V. palonosetron HCl pharmacokinetic data was obtained from a subset of pediatric cancer patients that received 10 mcg/kg or 20 mcg/kg. When the dose was increased from 10 mcg/kg to 20 mcg/kg a dose-proportional increase in mean AUC was observed. Following single dose intravenous infusion of palonosetron HCl 20 mcg/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 patients. Median half-life was 29.5 hours in overall age groups and ranged from about 20 to 30 hours across age groups after administration of 20 mcg/kg.

The total body clearance (L/h/kg) in patients 12 to 17 years old was similar to that in healthy adults. There are no apparent differences in volume of distribution when expressed as L/kg.

Table 8: Pharmacokinetic parameters in paediatric cancer patients following intravenous infusion of palonosetron at 20 mcg/kg over 15 min

Pk parameter [a]	**Paediatric age group**			
	< 2 y	**2 to < 6 y**	**6 to < 12 y**	**12 to < 17 y**
	N = 12	**N = 42**	**N = 38**	**N = 44**
C_T [b], ng/mL	9025 (197)	9414 (252)	16275 (203)	11831 (176)
		N = 5	**N = 7**	**N = 10**
$AUC_{0-\infty}$, h.mcg/L		103.5 (40.4)	98.7 (47.7)	124.5 (19.1)

	N = 6	N = 14	N = 13	N = 19
Clearance [c], L/h/kg	0.31 (34.7)	0.23 (51.3)	0.19 (46.8)	0.16 (27.8)
V_{ss}, L/kg	6.08 (36.5)	5.29 (57.8)	6.26 (40.0)	6.20 (29.0)

a Geometric mean (CV) except for t1/2 which is median values.
b CT is the plasma palonosetron concentration at the end on the15 minute infusion
c Clearance and Vss calculated from 10 and 20 mcg/kg and are weight adjusted

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

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 test or the mouse micronucleus test. It was, however, positive for clastogenic effects in the CHO cell chromosomal aberration test.

Carcinogenicity

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 150 to 289 times the human exposure at the recommended intravenous dose of 250 microgram.

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 lowest and highest doses, respectively, 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 in both male and female rats, of pancreatic Islet cell adenoma and combined adenoma and carcinoma of pancreatic acinar cell adenoma and combined adenoma and adenocarcinoma and of pituitary adenoma in male rats. Increased incidences of skin keratocanthomas and tail squamous cell papillomas were also observed, mainly in males. In female rats, palonosetron produced hepatocellular adenoma and combined hepatocellular adenoma and carcinoma, and increased the incidences of thyroid C-cell adenoma and combined adenoma and carcinoma, and of mammary gland adrenocarcinoma.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Mannitol

Citric acid monohydrate

Sodium citrate

Hydrochloric acid

Sodium hydroxide

Water for injection

6.2 INCOMPATIBILITIES

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

6.3 SHELF LIFE

24 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C. Protect from light. Do not freeze.

6.5 NATURE AND CONTENTS OF CONTAINER

Palonosetron – AFT solution for injection is supplied in a single use 6 mL Type I glass vial closed with a 20 mm brominated butyl rubber stopper and aluminium-plastic cap. One glass vial is packed in a carton.

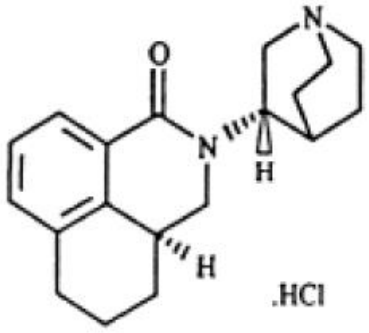
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Chemically, palonosetron hydrochloride is: (3aS)-2-[(S)-1-Azabicyclo[2.2.2]oct-3-yl]-2,3,3a,4,5,6-hexahydro-1-oxo-1Hbenz[de]isoquinoline hydrochloride. The empirical formula is $C_{19}H_{24}N_2O.HCl$, with a molecular weight of 332.87. Palonosetron hydrochloride exists as a single isomer.



CAS number

135729-61-2 Palonosetron

135729-62-3 Palonosetron Hydrochloride

7 MEDICINE CLASSIFICATION

S4 – Prescription only medicine

8 PRODUCT OWNER

AFT Pharmaceuticals Ltd.

129 Hurstmere Road

Takapuna, Auckland, New Zealand