ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Palonosetron Accord 250 micrograms solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

A clear colourless solution, practically free from foreign particles, pH 3.0 to 3.9, osmlolarity 260-320 mOsm/l.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Palonosetron Accord 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.

Palonosetron Accord 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

Palonosetron Accord 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. Palonosetron Accord should be injected over 30 seconds.

The efficacy of palonosetron 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 population
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.

Paediatric population

Children and adolescents (aged 1 month to 17 years):
20 micrograms/kg (the maximum total dose should not exceed 1,500 micrograms) palonosetron administered as a single 15 minutes intravenous infusion beginning approximately 30 minutes before the start of chemotherapy.

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

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

QT prolongation

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.

Interference with serotonergic medicinal products

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.

Other

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.

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

Excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per vial that is to say 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-HT_3 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

Summary of the safety profile

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 palonosetron, were headache (9 %) and constipation (5 %).

Tabulated list of adverse reactions

In the clinical studies the following adverse drug reactions (ADRs) were observed as possibly or probably related to palonosetron. These were classified as common (≥1/100 to <1/10) or uncommon (≥1/1,000 to <1/100). Very rare (<1/10,000) ADRs were reported post-marketing.
Within each frequency grouping, adverse reactions are presented below in order of decreasing seriousness.

System organ class	**Common ADRs (≥1/100 to<1/10)**	**Uncommon ADRs (≥1/1,000 to <1/100)**	**Very rare ADRs (<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	

* 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 ADRs (≥1/100 to <1/10)**	**Uncommon ADRs (≥1/1,000 to <1/100)**
Nervous system disorders	Headache	Dizziness, dyskinesia
Cardiac disorder		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 palonosetron, 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 palonosetron 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

Mechanism of action

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

Clinical efficacy and safety

In two randomised, double-blind studies with a total of 1,132 patients receiving moderately emetogenic chemotherapy that included cisplatin ≤50 mg/m^2, carboplatin, cyclophosphamide ≤1,500 mg/m^2 and doxorubicin >25 mg/m^2, palonosetron 250 micrograms and 750 micrograms were compared with ondansetron 32 mg (half-life 4 hours) or dolasetron 100 mg (half-life 7.3 hours) administered intravenously on Day 1, without dexamethasone.

In a randomised, double-blind study with a total of 667 patients receiving highly emetogenic chemotherapy that included cisplatin ≥ 60 mg/m^2, cyclophosphamide > 1,500 mg/m^2 and dacarbazine, palonosetron 250 micrograms and 750 micrograms were compared with ondansetron 32 mg administered intravenously on Day 1. Dexamethasone was administered prophylactically before chemotherapy in 67 % of patients.

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

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

Although comparative efficacy of palonosetron in multiple cycles has not been demonstrated in controlled clinical 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

	Palonosetron 250micrograms (n= 189)	Ondansetron 32milligrams (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 palonosetron and comparator.
c Chi-square test. Significance level at α=0.05.

Table 2: Percentage of patients a responding by treatment group and phase in the moderately emetogenic chemotherapy study versus dolasetron

	Palonosetron 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 palonosetron and comparator.
c Chi-square test. Significance level at α=0.05.

Table 3: Percentage of patients a responding by treatment group and phase in the highly emetogenic chemotherapy study versus ondansetron

	Palonosetron 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 palonosetron and comparator.
c Chi-square test. Significance level at α=0.05.

The effect of palonosetron on blood pressure, heart rate, and electrocardiogram (ECG) parameters including QTc were comparable to ondansetron and dolasetron in chemotherapy induced nausea and vomiting (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 intravenous 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 intravenously at single doses of 3mcg/kg and 10 mcg/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 mcg/kg compared to palonosetron 3 mcg/kg was 54.1 % and 37.1 % respectively.

The efficacy of palonosetron 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 intravenous 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 mcg/kg (maximum 0.75 mg), palonosetron 20 mcg/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-naive to chemotherapy (78.5 %) across all treatment groups. Emetogenic chemotherapies administered included doxorubicin, cyclophosphamide (<1500 mg/m^2), ifosfamide, cisplatin, dactinomycin, carboplatin, and daunorubicin. Adjuvant corticosteroids, including

dexamethasone, were administered with chemotherapy in 55 % of patients. The primary efficacy endpoint was Complete Response in the acute phase of the first cycle of chemotherapy, defined as no vomiting, no retching, and no rescue medication in the first 24 hours after starting chemotherapy. Efficacy was based on demonstrating non-inferiority of intravenous palonosetron compared to intravenous ondansetron. Non-inferiority criteria were met if the lower bound of the 97.5 % confidence interval for the difference in Complete Response rates of intravenous palonosetron minus intravenous ondansetron was larger than -15 %. In the palonosetron 10 mcg/kg, 20 mcg/kg and ondansetron groups, the proportion of patients with $CR_{0\text{-}24h}$ was 54.2 %, 59.4 % and 58.6 %. Since the 97.5 % confidence interval (stratum adjusted Mantel-Haenszel test) of the difference in $CR_{0\text{-}24h}$ between palonosetron 20 mcg/kg and ondansetron was [-11.7 %, 12.4 %], the 20 mcg/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 intravenously at single doses of 1mcg/kg and 3 mcg/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 16years 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 mcg/kg or 3 mcg/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 intravenous palonosetron (1 mcg/kg, max 0.075 mg) versus intravenous. 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 prespecified 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 (AUC0-∞) are generally dose-proportional over the dose range of 0.3–90 mcg/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 (AUC0-∞) 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 Cmax 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
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 population
Single-dose intravenous palonosetron pharmacokinetic data was obtained from a subset of paediatric cancer patients (n=280) 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 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 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 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 4: Pharmacokinetic parameters in paediatric cancer patients following intravenous infusion of palonosetron at 20 mcg/kg over 15 min and in Adult Cancer Patients receiving 3 and 10 mcg/kg palonosetron doses via intravenous bolus.

	Paediatric cancer patients[a]				**Adults cancer patients[b]**	
	<2y	**2 to <6 y**	**6 to <12 y**	**12 to <17 y**	**3.0 mcg/kg**	**10 mcg/kg**
	N=3	**N=5**	**N=7**	**N=10**	**N=6**	**N=5**
AUC0-∞, h.mcg/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 mcg /kg and 20 mcg /kg dose groups combined. In adults, different dose levels are indicated in column title.
[d] Vss (steady state) is reported for paediatric cancer patients, whereas Vz (elimination) 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 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 palonosetron 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,
Citric acid monohydrate,
Sodium citrate,
Disodium edetate,
Sodium hydroxide (for pH adjustment),
Hydrochloric acid, concentrated (for pH adjustment),
Water for injections.

6.2 Incompatibilities

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

6.3 Shelf life

3 years
Upon opening of the vial, it should be used immediately.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

6 ml type I tubular clear glass vial, closed with chlorobutyl rubber stopper and sealed with a flip-off aluminium seal.

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

6.6 Special precautions for disposal and other handling

Single use only, any unused solution should be discarded.

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

7. MARKETING AUTHORISATION HOLDER

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona, s/n,
Edifici Est 6ª planta,
08039 Barcelona,
Spain

8. MARKETING AUTHORISATION NUMBER

EU/1/16/1104/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26th May 2016
Date of latest renewal: 12 February 2021

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. MANUFACTURERS 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. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Accord Healthcare Polska Sp.z o.o.,
ul. Lutomierska 50,
95-200 Pabianice,
Poland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

  The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates 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 marketing authorisation holder (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.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Palonosetron Accord 250 micrograms solution for injection
palonosetron

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Excipients: mannitol, citric acid monohydrate, sodium citrate, disodium edetate, sodium hydroxide, hydrochloric acid concentrated, water for injections.

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

Discard any unused solution.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona, s/n,
Edifici Est 6ª planta,
08039 Barcelona,
Spain

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1104/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

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

LABEL

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

Palonosetron Accord 250 micrograms solution for injection
palonosetron

IV use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

250 mcg/5 ml

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

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

1. What Palonosetron Accord is and what it is used for

Palonosetron Accord contains the active substance palonosetron. This belongs to a group of medicines known as serotonin (5HT3) antagonists.

Palonosetron Accord is used in adults, adolescents and children over one month of age 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 Palonosetron Accord

Do not take Palonosetron Accord if:
- you are allergic to palonosetron or any of the other ingredients of this medicine (listed in section 6).

You will not be given Palonosetron Accord 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 Palonosetron Accord 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 Palonosetron Accord.

Other medicines and Palonosetron Accord
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 Selective serotonin reuptake inhibitors (SSRIs) - 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 Palonosetron Accord. 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 Palonosetron Accord – this is because these medicines could cause a heart beat problem when taken with Palonosetron Accord.

Pregnancy and breast-feeding

Pregnancy
If you are pregnant or think you might be pregnant, your doctor will not give you palonosetron accord unless it is clearly necessary. This is because we do not know if
Palonosetron accord 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 palonosetron accord 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.

Palonosetron Accord 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 Palonosetron Accord

Palonosetron Accord 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 palonosetron accord is 250 micrograms.
- It is given as a rapid injection into a vein.

Children and adolescents (aged 1 month to 17 years)
- The doctor will work out the right dose based on bodyweight.
- The maximum dose is 1,500 micrograms.
- Palonosetron accord will be given as a drip (a slow infusion into a vein).

It is not recommended you are given Palonosetron Accord 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 color of the vein and/or 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 movement
- abnormal heart rate
- cough and shortness of breath
- nose bleed
- 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 or pharmacist or nurse. 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 Palonosetron Accord

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 carton and the vial 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, dispose of any unused solution.

6. Contents of the pack and other information

What Palonosetron Accord contains
- The active substance is palonosetron (as hydrochloride).
  Each ml of solution contains 50 micrograms of palonosetron. Each vial of 5ml of solution contains 250 micrograms of palonosetron.
- The other ingredients are mannitol, disodium edetate, sodium citrate, citric acid monohydrate, sodium hydroxide (for pH adjustment), hydrochloric acid, concentrated (for pH adjustment) and water for injections. (See section 2 Palonosetron Accord contains sodium).

What Palonosetron Accord looks like and contents of the pack
Palonosetron Accord solution for injection is a clear, colourless solution supplied in a 6 ml glass vial, closed with chlorobutyl rubber stopper and sealed with a flip-off aluminium seal. Each vial contains one dose.

Pack size: one vial

Marketing Authorisation Holder
Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona, s/n,
Edifici Est 6ª planta,
08039 Barcelona,
Spain

Manufacturers

Accord Healthcare Polska Sp.z o.o.,
ul. Lutomierska 50,
95-200 Pabianice,
Poland

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Other sources of information

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