ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Akynzeo 300 mg/0.5 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 300 mg of netupitant and palonosetron hydrochloride equivalent to 0.5 mg of palonosetron.

Excipients with known effect

Each hard capsule contains 7 mg of sorbitol (E420) and 20 mg of sucrose.
It may also contain a trace of lecithin derived from soya.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule

Opaque gelatin capsule of size "0" (length 21.7 mm) with white body and caramel cap with "HE1" printed on the body. The hard capsule is filled with three tablets and one soft capsule.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Akynzeo is indicated in adults for the:
- Prevention of acute and delayed nausea and vomiting associated with highly emetogenic cisplatin-based cancer chemotherapy.
- Prevention of acute and delayed nausea and vomiting associated with moderately emetogenic cancer chemotherapy.

4.2 Posology and method of administration

Posology

One 300 mg/0.5 mg capsule should be administered approximately one hour prior to the start of each chemotherapy cycle.

The recommended oral dexamethasone dose should be reduced by approximately 50 % when co-administered with netupitant/palonosetron capsules (see section 4.5 and clinical studies administration schedule in section 5.1).

Special populations

Elderly people
No dose adjustment is necessary for elderly patients. Caution should be exercised when using this medicinal product in patients over 75 years, due to the long half-life of the active substances and the limited experience in this population.

Renal impairment

Dose adjustment is not considered necessary in patients with mild to severe renal impairment. Renal excretion for netupitant is negligible. Mild to moderate renal impairment does not significantly affect palonosetron pharmacokinetic parameters. Total systemic exposure to intravenous palonosetron increased by approximately 28% in severe renal impairment relative to healthy subjects. The pharmacokinetics of palonosetron or netupitant has not been studied in subjects with end-stage renal disease requiring hemodialysis and no data on the effectiveness or safety of netupitant/palonosetron capsules in these patients are available. Therefore, use in these patients should be avoided.

Hepatic impairment
No dose adjustment is necessary for patients with mild or moderate hepatic impairment (Child-Pugh score 5-8). Limited data exist in patients with severe hepatic impairment (Child Pugh score ≥ 9). As use in patients with severe hepatic impairment may be associated with increased exposure of netupitant, this medicinal product should be used with caution in these patients (see sections 4.4 and 5.2).

Paediatric population
The safety and efficacy of Akynzeo capsules in the paediatric population have not been established. No data are available.

Method of administration

For oral use.

The hard capsule should be swallowed whole and not opened as it contains 4 single pharmaceutical components that should be administered at the same time.

It can be taken with or without food.

4.3 Contraindications

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

Pregnancy (see section 4.6).

4.4 Special warnings and precautions for use

Constipation

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 (see section 4.8).

Serotonin syndrome

There have been reports of serotonin syndrome with the use of 5-HT_3 antagonists either alone or in combination with other serotonergic medicinal products (including selective serotonin reuptake inhibitors (SSRIs) and serotonin noradrenaline reuptake inhibitors (SNRIs). Appropriate observation of patients for serotonin syndrome-like symptoms is advised (see section 4.8).

QT Prolongation

An ECG study was conducted in adult male and female healthy volunteers with oral netupitant either 200 or 600 mg administered in combination with oral palonosetron 0.5 or 1.5 mg, respectively. The study demonstrated no clinically important effects on ECG parameters: the largest point estimate of the placebo and baseline corrected QTc interval was 7.0 ms (one-sided upper 95% confidence limit 8.8 ms), observed 16 hours after the administration of supratherapeutic doses (600 mg netupitant and 1.5 mg palonosetron). Upper 95% confidence limit of the point estimates of placebo

and baseline corrected QTcI was constantly within 10 ms at all time points over 2 days after study substance administration.

However, since netupitant/palonosetron capsules contains a 5-HT_3 receptor antagonist, caution should be exercised in concomitant use with medicinal products that increase the QT interval or 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, bradyarrhythmia, conduction disturbances and in patients taking anti-arrhythmic medicinal products or other medicinal products that lead to QT prolongation or electrolyte abnormalities. Hypokalaemia and hypomagnesaemia should be corrected prior to administration.

Caution should be exercised in patients with severe hepatic impairment since limited data are available in these patients.

This medicinal product should be used with caution in patients receiving concomitant orally administered active substances that are metabolised primarily through CYP3A4 and with a narrow therapeutic range (see section 4.5).

Chemotherapeutic agents that are substrates for CYP3A4

Netupitant is a moderate inhibitor of CYP3A4 and can increase the exposure of chemotherapeutic agents that are substrates for CYP3A4 e.g. docetaxel (see section 4.5). Therefore, patients should be monitored for increased toxicity of chemotherapeutic agents that are substrates for CYP3A4, including irinotecan. Furthermore, netupitant may also affect the efficacy of chemotherapeutic agents that need activation by CYP3A4 metabolism.

Excipients

This medicinal product contains 7 mg of sorbitol (E420) in each hard capsule.
The additive effect of concomitantly administered medicinal products containing sorbitol (E 420) (or fructose) and dietary intake of sorbitol (E 420) (or fructose) should be taken into account.
The content of sorbitol (E 420) in medicinal products for oral use may affect the bioavailability of other medicinal products for oral use administered concomitantly.

This medicinal product also contains 20 mg of sucrose in each capsule. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicinal product.

This medicinal product contains less than 1 mmol sodium per (23 mg) per hard capsule, that is to say essentially ‘sodium-free’.

It may also contain a trace of lecithin derived from soya. Therefore, patients with known hypersensitivity to peanut or soya should be monitored closely for signs of an allergic reaction (see section 4.8).

4.5 Interaction with other medicinal products and other forms of interaction

When netupitant/palonosetron capsules are used concomitantly with another CYP3A4 inhibitor, netupitant plasma concentrations could be elevated. When this medicinal product is used concomitantly with medicinal products that induce CYP3A4 activity, netupitant plasma concentrations could be reduced and this may result in decreased efficacy. This medicinal product can increase plasma concentrations of concomitantly administered medicinal products that are metabolised via CYP3A4.
In humans, netupitant is eliminated mainly by hepatic metabolism mediated by CYP3A4 with a marginal renal excretion. At a dose of 300 mg in humans, netupitant is a substrate and moderate inhibitor of CYP3A4. Palonosetron is eliminated from the body through both renal excretion and metabolic pathways, with the latter mediated via multiple CYP enzymes. 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.

Interaction between oral netupitant and oral palonosetron:

No clinically relevant pharmacokinetic interactions have been observed between oral netupitant and oral palonosetron.

Interaction with CYP3A4 substrates:

Dexamethasone
Co-administration of a single dose of 300 mg netupitant with a dexamethasone regimen (20 mg on Day 1, followed by 8 mg twice daily from Day 2 to Day 4) significantly increased the exposure to dexamethasone in a time and dose dependent manner. The AUC_{0-24} (Day 1), the AUC_{24-36} (Day 2) and the AUC_{84-108} and $AUC_{84-\infty}$ (Day 4) of dexamethasone increased 2.4-fold, with co-administration of 300 mg netupitant. The pharmacokinetic profile of netupitant was unchanged when administered in combination with dexamethasone.
As such, the oral dexamethasone dose should be reduced by approximately 50% when co-administered with netupitant/palonosetron capsules (see section 4.2).

Chemotherapeutic medicinal products (docetaxel, etoposide, cyclophosphamide)
Exposure to docetaxel and etoposide was increased 37% and 21%, respectively, when co-administered with netupitant/palonosetron capsules. No consistent effect was seen with cyclophosphamide after netupitant co-administration.

Oral contraceptives
Netupitant/palonosetron capsules, when given with a single oral dose of 60 mcg ethinylestradiol and 300 mcg levonorgestrel had no significant effect on the AUC of ethinylestradiol and increased the AUC of levonorgestrel by 1.4-fold; clinical effects on the efficacy of hormonal contraception are unlikely. No relevant changes of netupitant and palonosetron pharmacokinetics were observed.

Erythromycin and Midazolam
Exposure to erythromycin and midazolam was increased approximately 1.3 and 2.4 fold, respectively, when each was co-administered with netupitant. These effects were not considered clinically important. The pharmacokinetic profile of netupitant was unaffected by the concomitant administration of either midazolam or erythromycin. The potential effects of increased plasma concentrations of midazolam or other benzodiazepines metabolised via CYP3A4 (alprazolam, triazolam) should be considered when coadministering these active substances with netupitant/palonosetron capsules.

Serotonergic medicinal products (e.g. SSRIs and SNRIs)

There have been reports of serotonin syndrome following concomitant use of 5-HT_3 antagonists and other serotonergic medicinal products (including SSRIs such as fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram or escitalopram and SNRIs such as venlafaxine or duloxetine) (see section 4.4).

Effect of other medicinal products on the pharmacokinetics of Akynzeo

Netupitant is mainly metabolised by CYP3A4; therefore, co-administration with medicinal products that inhibit or induce CYP3A4 activity may influence plasma concentrations of netupitant. Consequently, concomitant administration with strong CYP3A4 inhibitors (e.g., ketoconazole) should be approached with caution and concomitant administration with strong CYP3A4 inducers (e.g., rifampicin) should be avoided. Moreover, this medicinal product should be used with caution in patients receiving concomitant orally administered active substances with a narrow therapeutic range that are primarily metabolised by CYP3A4, such as cyclosporine, tacrolimus, sirolimus, everolimus,

alfentanil, diergotamine, ergotamine, fentanyl, and quinidine.

Effect of ketoconazole and rifampicin

Administration of the CYP3A4 inhibitor ketoconazole with netupitant/palonosetron capsules increased the AUC of netupitant 1.8 fold and C_{max} 1.3 fold when compared to the administration of netupitant/palonosetron capsules alone. Co-administration with ketoconazole did not affect the pharmacokinetics of palonosetron.
Administration of the CYP3A4 inducer rifampicin with Akynzeo alone decreased the AUC of netupitant 5.2 fold and C_{max} 2.6 fold. Co-administration of rifampicin did not affect the pharmacokinetics of palonosetron. Consequently, concomitant administration with strong CYP3A4 inhibitors (e.g., ketoconazole) should be approached with caution and concomitant administration with strong CYP3A4 inducers (e.g. rifampicin) should be avoided.

Additional interactions

Netupitant/palonosetron capsules are unlikely to interact with medicinal products which are P-gp substrates. Netupitant is not a substrate for P-gp. When netupitant was administered on Day 8 of a 12-day regimen of digoxin, no changes in digoxin pharmacokinetics were observed.
Inhibition of the efflux transported BCRP and glucuronidation isozyme UGT2B7 by netupitant and its metabolites is unlikely and, if it occurs, of scarce clinical relevance.
In vitro data shows that netupitant inhibits UGT2B7, the magnitude of such an effect in the clinical setting is not established. Caution is recommended when netupitant is combined with an oral substrate of this enzyme (e.g.zidovudine, valproic acid, morphine).
In vitro data suggests that netupitant inhibits the efflux of transporter BCRP. The clinical relevance of this effect is not established.
In vitro data show that netupitant is a P-gp inhibitor. In a study performed in healthy volunteers, netupitant does not affect the exposure of digoxin, a P-gp substrate, whereas it increases its Cmax by 1.09 fold [90%CI 0.9-1.31]. It is not excluded that this effect may be more marked, and then clinically relevant, in cancer patients, notably those having abnormal renal function. Therefore, caution is recommended when netupitant is combined with digoxin or with other P-gp substrates such as dabigatran, or colchicine.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/ contraception in females

Women of childbearing potential should not be pregnant or become pregnant while on treatment with netupitant/palonosetron capsules. A pregnancy test should be performed on all pre-menopausal women prior to treatment. Women of childbearing potential must use effective contraception during therapy and up to one month after treatment with this medicinal product.

Pregnancy

Netupitant
There are no data about the use of netupitant in pregnant women. Studies in animals have shown reproductive toxicity including teratogenic effects in rabbit without safety margin (see section 5.3).

Palonosetron
There are no data about the use of palonosetron in pregnant women. Animal data do not indicate direct or indirect harmful effects of palonosetron with the respect to reproductive toxicity (see section 5.3).

Netupitant/palonosetron capsules are contraindicated during pregnancy (see section 4.3).

Breast-feeding

It is unknown whether palonosetron or netupitant are excreted in human milk. A risk to the suckling child cannot be excluded. Netupitant/palonosetron capsules should not be used during breast-feeding. Breast-feeding should be discontinued during treatment with this medicinal product and for 1 month after the last dose.

Fertility

Netupitant
No effect on fertility has been observed in animal studies.

Palonosetron
Degeneration of seminiferous epithelium has been observed in rat study (see section 5.3).

4.7 Effects on ability to drive and use machines

Netupitant/palonosetron capsules have moderate influence on the ability to drive and use machines. Since it may induce dizziness, somnolence or fatigue, patients should be cautioned not to drive or use machines if such symptoms occur.

4.8 Undesirable effects

Summary of the safety profile

Common adverse reactions reported with netupitant/palonosetron capsules were headache (3.6%), constipation (3.0%) and fatigue (1.2%).

Tabulated list of adverse reactions

Adverse reactions are listed below by MedDRA body system organ class and frequency.

The following convention has been used for classification of frequency:
Very common (≥1/10),
Common (≥1/100 to <1/10),
Uncommon (≥1/1 000 to <1/100),
Rare (≥1/10 000 to <1/1 000),
Very rare (<1/10 000),
Not known (cannot be estimated from the available data).

Table1: Adverse reactions

System organ class	Common	Uncommon	Rare
Infections and infestations			Cystitis
Blood and lymphatic system disorders		Neutropenia	Leukopenia
		Leucocytosis	Lymphocytosis
Metabolism and nutrition disorders		Decreased appetite	Hypokalaemia
Psychiatric disorders		Insomnia	Acute psychosis
			Mood altered
			Sleep disorder
Nervous system disorders	Headache	Dizziness	Hypoaesthesia
			Somnolence
Eye disorders			Conjunctivitis
			Vision blurred
Ear and labyrinth disorders		Vertigo	Tinnitus
Cardiac disorders		Atrioventricular block first degree	Arrhythmia
		Cardiomyopathy	Atrioventricular block second degree
		Conduction disorder	Bundle branch block left
		Tachycardia	Bundle branch block right
			Mitral valve incompetence
			Myocardial ischaemia
			Ventricular extrasystoles
Vascular disorders		Hypertension	Flushing
			Hypotension
Respiratory, thoracic and mediastinal disorders		Hiccups	
Gastrointestinal disorders	Constipation	Abdominal distension	Dry mouth
		Abdominal pain	Dysphagia
		Diarrhoea	Eructation
		Dyspepsia	Haemorrhoids
		Flatulence	Tongue coated
		Nausea	Vomiting
Skin and subcutaneous tissue disorders		Alopecia	Erythema
		Urticaria	Pruritus
			Rash
Musculoskeletal and connective tissue disorders			Back pain
			Pain in extremities
General disorders and administration site conditions	Fatigue	Asthenia	Feeling hot
			Non-cardiac chest pain
			Product taste abnormal
Investigations		Liver transaminases increased	Blood bilirubin increased
		Blood alkaline phosphatase increased	Blood creatine phosphokinase increased
		Blood creatinine	Blood creatine phosphokinase

		increased	MB increased
		Electrocardiogram QT prolonged	Blood urea increased
			Electrocardiogram ST segment depression
			Electrocardiogram ST-T segment abnormal
			Myoglobin blood increased
			Neutrophil count increased
			Troponin increased

Post-marketing data indicates that the adverse reactions profile is generally similar to that seen in clinical trials.

Description of selected adverse reactions

Netupitant:
No common adverse reactions are attributable to netupitant, the new component of the fixed combination.

Palonosetron:
Cases of constipation with faecal impaction requiring hospitalisation have been reported in association with palonosetron 0.75 mg.

In addition, eye swelling, dyspnoea and myalgia as adverse reactions have been reported with oral palonosetron but not observed during the development of this medicinal product. All these reactions were uncommon.

Very rare cases of anaphylaxis, anaphylactic/anaphylactoid reactions and shock have been reported from the post-marketing use of intravenous palonosetron. The signs may include hives, itch, angioedema, low blood pressure, throat tightness, chest tightness, dyspnoea, loss of consciousness.

There have also been reports of serotonin syndrome. The signs may include tremor, agitation, sweating, myoclonic movements, hypertonia and fever.

Netupitant and palonosetron combinate capsule:

This medicinal product may contain a trace of lecithin derived from soya. Therefore, patients with known hypersensitivity to peanut or soya should be monitored closely for signs of an allergic reaction. The signs may include hives, skin rash, itching, difficulty breathing or swallowing, swollen mouth, face, lips, tongue or throat and sometimes a drop-in blood pressure.

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

Based on the experience with healthy subjects exposed to oral netupitant 600 mg in combination with palonosetron 1.50 mg the potential acute symptoms of overdose are headache, dizziness, constipation, anxiety, palpitations, euphoric mood and pain in the legs. In case of overdose, the medicinal product should be discontinued and general supportive treatment and monitoring should be provided. Because of the antiemetic activity of netupitant and palonosetron, emesis induced by a

medicinal product may not be effective. Dialysis studies have not been performed. However, due to the large volume of distribution of palonosetron and netupitant, dialysis is unlikely to be an effective treatment for overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiemetics and antinauseants, serotonin (5-HT_3) antagonists; ATC code: A04AA55

Mechanism of action

Netupitant is a selective antagonist of human substance P/neurokinin 1 (NK_1) receptors. Palonosetron is a 5-HT_3 receptor antagonist with a strong binding affinity for this receptor and little or no affinity for other receptors. Chemotherapeutic substances produce nausea and vomiting by stimulating the release of serotonin from the enterochromaffin cells of the small intestine. Serotonin then activates 5-HT_3 receptors located on vagal afferents to initiate the vomiting reflex.

Delayed emesis has been associated with the activation of tachykinin family neurokinin 1 (NK_1) receptors (broadly distributed in the central and peripheral nervous systems) by substance P. As shown in *in vitro* and *in vivo* studies, netupitant inhibits substance P mediated responses.

Netupitant was shown to cross the blood brain barrier with a NK_1 receptor occupancy of 92.5%, 86.5%, 85.0%, 78.0%, and 76.0% in striatum at 6, 24, 48, 72, and 96 hours, respectively, after administration of 300 mg netupitant.

Clinical efficacy and safety

Oral administration of Akynzeo in combination with dexamethasone has been shown to prevent acute and delayed nausea and vomiting associated with highly and moderately emetogenic cancer chemotherapy in two separate pivotal studies.

Highly Emetogenic Chemotherapy (HEC) study
In a multicenter, randomized, parallel, double-blind, controlled clinical study of 694 patients, the efficacy and safety of single doses of oral netupitant in combination with oral palonosetron was compared with a single oral dose of palonosetron in cancer patients receiving a chemotherapy regimen that included cisplatin (median dose = 75 mg/m^2). The efficacy of Akynzeo was assessed in 135 patients who received a single oral dose (netupitant 300 mg and palonosetron 0.5 mg) and 136 patients who received oral palonosetron 0.5 mg alone.

Treatment regimens for the Akynzeo and the palonosetron 0.5 mg arms are displayed in Table below.

Table 2: Oral antiemetic treatment regimen — HEC study

Treatment regimen	Day 1	Days 2 to 4
Akynzeo	Akynzeo (Netupitant 300 mg + Palonosetron 0.5 mg) Dexamethasone 12 mg	Dexamethasone 8 mg once a day
Palonosetron	Palonosetron 0.5 mg Dexamethasone 20 mg	Dexamethasone 8 mg twice a day

The primary efficacy endpoint was complete response (CR) rate (defined as no emetic episodes, no rescue medication) within 120 hours (overall phase) after the start of the highly emetogenic chemotherapy administration.
A summary of the key results from this study is shown in Table 3 below.

Table 3: Proportion of patients receiving cisplatin chemotherapy responding by treatment group and phase

	Akynzeo N=135 %	Palonosetron 0.5 mg N=136 %	p-value
Primary endpoint			
Complete response			
Overall phase[§]	89.6	76.5	0.004
Major secondary endpoints			
Complete response			
Acute phase[‡]	98.5	89.7	0.007
Delayed phase[†]	90.4	80.1	0.018
No emesis			
Acute phase	98.5	89.7	0.007
Delayed phase	91.9	80.1	0.006
Overall phase	91.1	76.5	0.001
No significant nausea			
Acute phase	98.5	93.4	0.050
Delayed phase	90.4	80.9	0.004
Overall phase	89.6	79.4	0.021

[‡]Acute phase: 0 to 24 hours post-cisplatin treatment.
[†]Delayed phase: 25 to 120 hours post-cisplatin treatment.
[§]Overall: 0 to 120 hours post-cisplatin treatment.

Moderately Emetogenic Chemotherapy (MEC) study
In a multicenter, randomized, parallel, double-blind, active-controlled, superiority study, the efficacy and safety of a single oral dose of Akynzeo was compared with a single oral dose of palonosetron 0.5 mg in cancer patients scheduled to receive the first cycle of an anthracycline and cyclophosphamide regimen for the treatment of a solid malignant tumour. At the time of the study, anthracycline-cyclophosphamide containing chemotherapy regimens were considered to be moderately emetogenic. Recent guidance has updated these regimens to highly emetogenic.
All patients received a single oral dose of dexamethasone.

Table 4: Oral antiemetic treatment regimen – MEC study

Treatment regimen	**Day 1**	**Days 2 to 3**
Akynzeo	Akynzeo Netupitant 300 mg Palonosetron 0.5 mg Dexamethasone 12 mg	No antiemetic treatment
Palonosetron	Palonosetron 0.5 mg Dexamethasone 20 mg	No antiemetic treatment

After completion of cycle 1, patients had the option to participate in a multiple-cycle extension, receiving the same treatment as assigned in cycle 1. There was no pre-specified limit of the number of repeat consecutive cycles for any patient. A total of 1450 patients (Akynzeo n=725; Palonosetron n=725) received study medication. Of these, 1438 patients (98.8%) completed cycle 1 and

1286 patients (88.4%) continued treatment in the multiple-cycle extension. A total of 907 patients (62.3%) completed the multiple-cycle extension up to a maximum of eight treatment cycles.
A total of 724 patients (99.9%) were treated with cyclophosphamide. All patients were additionally treated with either doxorubicin (68.0%) or epirubicin (32.0%).

The primary efficacy endpoint was the CR rate in the delayed phase, 25-120 hours after the start of the chemotherapy administration.

A summary of the key results from this study is shown in Table below.

Table 5: Proportion of patients receiving anthracycline and cyclophosphamide chemotherapy responding by treatment group and phase – cycle 1

	Akynzeo N=724 %	Palonosetron 0.5 mg N=725 %	p-value*
Primary endpoint			
Complete response			
Delayed phase[†]	76.9	69.5	0.001
Major secondary endpoints			
Complete response			
Acute phase[‡]	88.4	85.0	0.047
Overall phase[§]	74.3	66.6	0.001
No emesis			
Acute phase	90.9	87.3	0.025
Delayed phase	81.8	75.6	0.004
Overall phase	79.8	72.1	<0.001
No significant nausea			
Acute phase	87.3	87.9	N.S.
Delayed phase	76.9	71.3	0.014
Overall phase	74.6	69.1	0.020

* p-value from Cochran-Mantel-Haenszel test, stratified by age class and region.
[‡]Acute phase: 0 to 24 hours after anthracycline and cyclophosphamide regimen
[†]Delayed phase: 25 to 120 hours after anthracycline and cyclophosphamide regimen
[§]Overall: 0 to 120 hours after anthracycline and cyclophosphamide regimen

Patients continued into the Multiple-Cycle extension for up to 7 additional cycles of chemotherapy. Antiemetic activity of Akynzeo was maintained throughout repeat cycles for those patients continuing in each of the multiple cycles.
The impact of nausea and vomiting on patients' daily lives was assessed using the Functional Living Index–Emesis (FLIE). The proportion of patients with Overall no impact on daily life was 6.3% higher (p value =0.005) in the Akynzeo group (78.5%) than in the palonosetron group (72.1%).

Multiple-cycle safety study in patients receiving either Highly Emetogenic Chemotherapy or Moderately Emetogenic Chemotherapy
In a separate study, a total of 413 patients undergoing initial and repeat cycles of chemotherapy (including carboplatin, cisplatin, oxaliplatin, and doxorubicin regimens), were randomized to receive either Akynzeo (n=309) or aprepitant and palonosetron (n=104). Safety and efficacy were maintained throughout all cycles.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Akynzeo in all subsets of the paediatric population in prevention of acute and delayed nausea and vomiting associated with highly emetogenic cisplatin-based and moderately emetogenic cancer chemotherapy (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Netupitant
Absolute netupitant bioavailability data are not available in humans; based on data from two studies with intravenous netupitant, the bioavailability in humans is estimated to be greater than 60%.
In single dose oral studies, netupitant was measurable in plasma between 15 minutes and 3 hours after dosing. Plasma concentrations followed a first order absorption process and reached C_{max} in approximately 5 hours. There was a supra-proportional increase in C_{max} and AUC parameters for doses from 10 mg to 300 mg.
In 82 healthy subjects given a single oral dose of netupitant 300 mg, maximum plasma netupitant concentration (C_{max}) was 486 ±268 ng/mL (mean ± SD) and median time to maximum concentration (T_{max}) was 5.25 hours, the AUC was 15032 ± 6858 h.ng/mL. In a pooled analysis, females had a higher netupitant exposure compared to males; there was a 1.31-fold increase in C_{max}, a 1.02 fold increase for AUC and a 1.36 fold increase in half-life.
Netupitant $AUC_{0-\infty}$ and C_{max} increased by 1.1 fold and 1.2 fold, respectively, after a high fat meal.

Palonosetron
Following oral administration, palonosetron is well absorbed with its absolute bioavailability reaching 97%. After single oral doses using buffered solution mean maximum palonosetron concentrations (C_{max}) and area under the concentration-time curve ($AUC_{0-\infty}$) were dose proportional over the dose range of 3.0 to 80 mcg/kg in healthy subjects.
In 36 healthy male and female subjects given a single oral dose of 0.5 mg palonosetron, maximum plasma concentration (C_{max}) was 0.81 ± 1.66 ng/mL (mean ± SD) and time to maximum concentration (T_{max}) was 5.1 ± 1.7 hours. In female subjects (n=18), the mean AUC was 35% higher and the mean C_{max} was 26% higher than in male subjects (n=18). In 12 cancer patients given a single oral dose of palonosetron 0.5 mg one hour prior to chemotherapy, C_{max} was 0.93 ± 0.34 ng/mL and T_{max} was 5.1 ± 5.9 hours. The AUC was 30% higher in cancer patients than in healthy subjects. A high fat meal did not affect the C_{max} and AUC of oral palonosetron.

Distribution

Netupitant
After a single oral 300 mg dose administration in cancer patients, netupitant disposition was characterised by a two compartment model with an estimated median systemic clearance of 20.5 L/h and a large distribution volume in the central compartment (486 L). Human plasma protein binding of netupitant and its two major metabolites M1 and M3 is > 99% at concentrations ranging from 10 to 1500 ng/mL. The third major metabolite, M2, is > 97% bound to plasma proteins.

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

Biotransformation

Netupitant
Three metabolites have been detected in human plasma at netupitant oral doses of 30 mg and higher (the desmethyl derivative, M1; the N-oxide derivative, M2; the OH-methyl derivative, M3). *In vitro*

metabolism studies have suggested that CYP3A4 and, to a lesser extent, CYP2D6 and CYP2C9 are involved in the metabolism of netupitant. After administration of a single oral dose of 300 mg netupitant, mean plasma netupitant/plasma radioactivity ratios ranged from 0.13 to 0.49 over 96 h post-dose. The ratios were time dependent with values decreasing gradually beyond 24 h post-dose, indicating that netupitant is being rapidly metabolised. Mean C_{max} was approximately 11%, 47% and 16% of the parent for M1, M2 and M3 respectively; M2 had the lowest AUC relative to the parent (14%) whereas M1 and M3 AUC were approximately 29% and 33% of the parent, respectively. M1, M2 and M3 metabolites were all shown to be pharmacologically active in an animal pharmacodynamic model, where M3 was most potent and M2 least active.

Palonosetron
Palonosetron is eliminated by multiple routes with approximately 50% metabolised to form two primary metabolites: N-oxide-palonosetron and 6-S-hydroxy-palonosetron. These metabolites each have less than 1% of the 5-HT_3 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

Netupitant
Following administration of a single dose of Akynzeo, netupitant is eliminated from the body in a multi-exponential fashion, with an apparent mean elimination half-life of 88 hours in cancer patients. Renal clearance is not a significant elimination route for netupitant-related entities. The mean fraction of an oral dose of netupitant excreted unchanged in urine is less than 1%; a total of 3.95% and 70.7% of the radioactive dose was recovered in the urine and faeces, respectively. Approximately half the radioactivity administered orally as [14C]-netupitant was recovered from urine and faeces within 120 h of dosing. Elimination via both routes was estimated to be complete by Day 29-30 post-dose.

Palonosetron
Following administration of a single oral 0.75 mg dose of [14C]-palonosetron to six healthy subjects, 85% to 93% of the total radioactivity was excreted in urine, and 5% to 8% was eliminated in faeces. The amount of unchanged palonosetron excreted in the urine represented approximately 40% of the administered dose. In healthy subjects given palonosetron capsules 0.5 mg, the terminal elimination half-life (t½) of palonosetron was 37 ± 12 hours (mean ± SD), and in cancer patients, t½ was 48 ± 19 hours. After a single dose of approximately 0.75 mg intravenous palonosetron, the total body clearance of palonosetron in healthy subjects was 160 ± 35 mL/h/kg (mean ± SD) and renal clearance was 66.5± 18.2 mL/h/kg.

Special populations

Hepatic impairment

Netupitant
Maximum concentrations and total exposure of netupitant were increased in subjects with mild (n=8), moderate (n=8), and severe (n=2) hepatic impairment compared to matching healthy subjects, although there was pronounced individual variability in both hepatically-impaired and healthy subjects. Exposure to netupitant (C_{max}, AUC_{0-t} and $AUC_{0-\infty}$) compared to matching healthy subjects was 11%, 28% and 19% higher in mild and 70%, 88% and 143% higher in moderate hepatically-impaired subjects, respectively. As such, no dose adjustment is necessary for patients with mild to moderate hepatic impairment. Limited data exist in patients with severe hepatic impairment (Child Pugh score ≥9).

Palonosetron
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.

Renal impairment

Netupitant
No specific studies were performed to evaluate netupitant in patients with renal impairment. In the ADME trial, less than 5% of all netupitant-related material was excreted in urine and less than 1% of the netupitant dose was eliminated unchanged in the urine and therefore any accumulation of netupitant or metabolites after a single dose would be negligible. Furthermore, the population PK study showed no correlation between PK parameters of netupitant and markers of renal dysfunction.

Palonosetron
Mild to moderate renal impairment does not significantly affect palonosetron PK parameters. Total systemic exposure to intravenous palonosetron increased by approximately 28% in patients with severe impairment relative to healthy subjects. In a population PK study, patients with a reduced creatinine clearance (CL_{CR}) also had a reduced palonosetron clearance, but this reduction would not result in a significant change in palonosetron exposure.

Therefore, Akynzeo can be administered without dose adjustment in patients with renal impairment.

Neither netupitant nor palonosetron have been evaluated in patients with end-stage renal disease.

5.3 Preclinical safety data

Palonosetron

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. Degeneration of seminiferous epithelium was associated with palonosetron following a one month oral repeat dose toxicity study in rats. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. Only limited data from animal studies are available regarding the placental transfer (see section 4.6). Palonosetron is not mutagenic. High doses of palonosetron (each dose causing at least 15 times the human therapeutic exposure) applied daily for two years caused an increased rate of liver tumours, endocrine neoplasms (in thyroid, pituitary, pancreas, adrenal medulla) and skin tumours in rats but not in mice. The underlying mechanisms are not fully understood, but because of the high doses employed and since the medicinal product is intended for single application in humans, these findings are not considered relevant for clinical use.

Netupitant and combination with palonosetron

Effects in non-clinical studies based on safety pharmacology and single and repeated dose toxicity were observed only at exposures considered in excess of the maximum human exposure, indicating little relevance to clinical use. Phospholipidosis (foamy macrophages) has been observed with the administration of netupitant after repeated administration in rats and dogs. The effects were reversible or partially reversible after the recovery period. The significance of these findings in humans is unknown.

Non-clinical studies indicate that netupitant and its metabolites and the combination with palonosetron only at very high concentrations may block ion channels involved in ventricular de- and re-polarisation and prolong action potential duration. Reproductive studies in animals with netupitant do not indicate direct or indirect harmful effects with respect to fertility, parturition or postnatal development. An increased incidence of positional foetal abnormalities of the limbs and paws, fused sternebrae and agenesis of accessory lung lobe were observed following daily administration of

netupitant in rabbits at 10 mg/kg/day and higher during the period of organogenesis. In a pilot dose range finding study in rabbits, cleft palate, microphtalmia and aphakia were observed in four foetuses from one litter in the 30 mg/kg/day group. The relevance of these findings in humans is unknown. No data from animal studies with netupitant are available regarding placental transfer and lactation. Netupitant is not mutagenic.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hard capsule content

Netupitant tablets
Microcrystalline cellulose (E460)
Sucrose lauric acid esters
Povidone K-30
Croscarmellose sodium
Colloidal hydrated silica
Sodium stearyl fumarate
Magnesium stearate

Palonosetron soft capsules
Soft capsule content
Glycerol monocaprylocaprate (type I)
Glycerol
Polyglyceryl oleate
Purified water
Butylhydroxyanisole (E320)

Soft capsule shell
Gelatin
Glycerol
Sorbitol (E420)
1,4 sorbitan
Titanium dioxide (E171)

Hard capsule shell

Gelatin
Titanium dioxide (E171)
Yellow iron oxide (E172)
Red iron oxide (E172)

Printing ink
Shellac glaze (partially esterified)
Black iron oxide (E172)
Propylene glycol (E1520)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Alu/Alu blister.

Pack size of one hard capsule or 4 x1 hard capsules in perforated unit dose blisters.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Helsinn Birex Pharmaceuticals Ltd.
Damastown
Mulhuddart
Dublin 15
Ireland.

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1001/001
EU/1/15/1001/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27 May 2015
Date of latest renewal: 9 January 2020

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Akynzeo 235 mg/0.25 mg powder for concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 235 mg of fosnetupitant (as chloride hydrochloride), which corresponds to 197.5 mg of netupitant, and 0.25 mg of palonosetron (as hydrochloride).

After reconstitution and dilution 1 ml of solution contains 4.7 mg fosnetupitant, which corresponds to 3.95 mg of netupitant, and 0.005 mg palonosetron.

Excipients with known effect

Each vial contains approximately 24.8 mg of sodium.
If reconstituted and diluted with sodium chloride 9 mg/ml (0.9%) solution for injection, the final solution contains approximately 202 mg of sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.

White to off-white amorphous powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Akynzeo is indicated in adults for the:
- Prevention of acute and delayed nausea and vomiting associated with highly emetogenic cisplatin-based cancer chemotherapy.
- Prevention of acute and delayed nausea and vomiting associated with moderately emetogenic cancer chemotherapy.

4.2 Posology and method of administration

Posology

The recommended dose is 235 mg/0.25 mg (the content of one vial of powder, reconstituted and diluted) administered as an infusion over 30 minutes, initiated approximately 30 minutes prior to the start of each chemotherapy cycle (see section 6.6).
At the end of the infusion, the infusion line should be flushed with the same carrier solution to ensure complete medicinal product administration.

The recommended oral dexamethasone dose should be reduced by approximately 50 % when co-administered with fosnetupitant and palonosetron hydrochloride combination (see section 4.5 and clinical studies administration schedule in section 5.1).

Special populations

Elderly people
No dose adjustment is necessary for elderly patients. Caution should be exercised when using this medicinal product in patients over 75 years, due to the long half-life of the active substances and the limited experience in this population.

Renal impairment
Dose adjustment is not considered necessary in patients with mild to severe renal impairment. Renal excretion for netupitant is negligible. Mild to moderate renal impairment does not significantly affect palonosetron pharmacokinetic parameters. Total systemic exposure to intravenous palonosetron increased by approximately 28% in severe renal impairment relative to healthy subjects. The pharmacokinetics of palonosetron or netupitant have not been studied in subjects with end-stage renal disease requiring hemodialysis and no data on the effectiveness or safety of fosnetupitant and palonosetron hydrochloride combination in these patients are available. Therefore, the use in these patients should be avoided.

Hepatic impairment
No dose adjustment is necessary for patients with mild or moderate hepatic impairment (Child-Pugh score 5-8). Limited data exist in patients with severe hepatic impairment (Child Pugh score ≥ 9). As use in patients with severe hepatic impairment may be associated with increased exposure of netupitant, this medicinal product should be used with caution in these patients (see sections 4.4 and 5.2).

Paediatric population
The safety and efficacy of Akynzeo in children aged 1 month to less than 18 years have not yet been established. No data are available.

Method of administration

This medicinal product should be administered intravenously. Intravenous administration occurs preferably through a running intravenous infusion over 30 minutes (see section 6.6).

For instructions on reconstitution and dilution of the medicinal product before administration, see Section 6.6.

4.3 Contraindications

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

Pregnancy (see section 4.6).

4.4 Special warnings and precautions for use

Constipation

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 (see section 4.8).

Serotonin syndrome

There have been reports of serotonin syndrome with the use of 5-HT_3 antagonists either alone or in combination with other serotonergic medicinal products (including selective serotonin reuptake inhibitors (SSRIs) and serotonin noradrenaline reuptake inhibitors (SNRIs). Appropriate observation of patients for serotonin syndrome-like symptoms is advised (see section 4.8).

QT Prolongation

An ECG study was conducted in adult male and female healthy volunteers with oral netupitant either 200 mg or 600 mg administered in combination with oral palonosetron 0.5 mg or 1.5 mg, respectively. The study demonstrated no clinically important effects on ECG parameters: the largest point estimate of the placebo and baseline corrected QTc interval was 7.0 ms (one-sided upper 95% confidence limit 8.8 ms), observed 16 hours after the administration of supratherapeutic doses (600 mg netupitant and 1.5 mg palonosetron). The upper 95% confidence limit of the point estimates of placebo and baseline corrected QTcI was constantly within 10 ms at all time points over 2 days after study administration of the medicinal product.

However, since netupitant and palonosetron hydrochloride combination contains a 5-HT_3 receptor antagonist, caution should be exercised in concomitant use with medicinal products that increase the QT interval or 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, bradyarrhythmia, conduction disturbances and in patients taking anti-arrhythmic medicinal products or other medicinal products that lead to QT prolongation or electrolyte abnormalities. Hypokalaemia and hypomagnesaemia should be corrected prior to administration.

This medicinal product should not be used to prevent nausea and vomiting in the days following chemotherapy if not associated with another chemotherapy administration.

It should not be used to treat nausea and vomiting following chemotherapy.

Caution should be exercised in patients with severe hepatic impairment since limited data are available in these patients.

This medicinal product should be used with caution in patients receiving concomitant orally administered active substances that are metabolised primarily through CYP3A4 and with a narrow therapeutic range (see section 4.5).

Chemotherapeutic agents that are substrates for CYP3A4

Netupitant is a moderate inhibitor of CYP3A4 and can increase the exposure of chemotherapeutic agents that are substrates for CYP3A4, e.g. docetaxel (see section 4.5). Therefore, patients should be monitored for increased toxicity of chemotherapeutic agents that are substrates for CYP3A4, including irinotecan. Furthermore, netupitant may also affect the efficacy of chemotherapeutic agents that need activation by CYP3A4 metabolism.

Excipients

This medicinal product contains approximately 24.8 mg of sodium per vial, equivalent to 1.24% of the WHO recommended maximum daily intake of 2 g sodium for an adult.
If reconstituted and diluted with sodium chloride 9 mg/ml (0.9%) solution for injection, the final solution contains approximately 202 mg of sodium per dose, equivalent to 10.1% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interactions

When administered intravenously fosnetupitant is rapidly converted to netupitant.
Interactions with other medicinal products following administration of intravenous fosnetupitant are likely to occur with active substances that interact with oral netupitant. The following information was derived from studies conducted with oral netupitant and studies conducted with intravenous fosnetupitant.

In humans, netupitant is eliminated mainly by hepatic metabolism mediated by CYP3A4 with a marginal renal excretion. At a dose of 300 mg in humans, netupitant is a substrate and moderate inhibitor of CYP3A4. Palonosetron is eliminated from the body through both renal excretion and metabolic pathways, with the latter mediated via multiple CYP enzymes. 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.

Interaction between oral netupitant and oral palonosetron

No clinically relevant pharmacokinetic interactions have been observed between oral netupitant and oral palonosetron.

Interaction with CYP3A4 substrates

Dexamethasone
Co-administration of a single oral dose of 300 mg netupitant or a single intravenous dose of 235 mg fosnetupitant with a dexamethasone regimen (20 mg on Day 1, followed by 8 mg twice daily from Day 2 to Day 4) significantly increased the exposure to dexamethasone in a time and dose dependent manner. The $AUC_{84-\infty}$ (Day 4) of dexamethasone increased 2.4-fold with co-administration of 300 mg netupitant or 235 mg fosnetupitant. The pharmacokinetic profile of netupitant was unchanged when administered in combination with dexamethasone.
As such, the oral dexamethasone dose should be reduced by approximately 50% when co-administered with fosnetupitant and palonosetron hydrochloride combination (see section 4.2).

Chemotherapeutic medicinal products (docetaxel, etoposide, cyclophosphamide)
Exposure to docetaxel and etoposide was increased 37% and 21%, respectively, when co-administered with netupitant/palonosetron capsules. No consistent effect was seen with cyclophosphamide after netupitant co-administration.

Oral contraceptives
Netupitant/palonosetron capsules, when given with a single oral dose of 60 mcg ethinylestradiol and 300 mcg levonorgestrel had no significant effect on the AUC of ethinylestradiol and increased the AUC of levonorgestrel by 1.4-fold; clinical effects on the efficacy of hormonal contraception are unlikely. No relevant changes of netupitant and palonosetron pharmacokinetics were observed.

Erythromycin and Midazolam
Exposure to erythromycin and midazolam was increased approximately 1.3 and 2.4 fold, respectively, when each was co-administered with netupitant administered orally. These effects were not considered clinically important. The pharmacokinetic profile of netupitant was unaffected by the concomitant administration of either midazolam or erythromycin. The potential effects of increased plasma concentrations of midazolam or other benzodiazepines metabolised via CYP3A4 (alprazolam, triazolam) should be considered when coadministering these active substances with netupitant and palonosetron hydrochloride combination.

Serotonergic medicinal products (e.g. SSRIs and SNRIs)

There have been reports of serotonin syndrome following concomitant use of 5-HT_3 antagonists and other serotonergic medicinal products (including SSRIs such as fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram or escitalopram and SNRIs such as venlafaxine or duloxetine) (see section 4.4).

Effect of other medicinal products on the pharmacokinetics of Akynzeo

Netupitant is mainly metabolised by CYP3A4; therefore, co-administration with medicinal products that inhibit or induce CYP3A4 activity may influence plasma concentrations of netupitant. Consequently, concomitant administration with strong CYP3A4 inhibitors (e.g., ketoconazole) should

be approached with caution and concomitant administration with strong CYP3A4 inducers (e.g., rifampicin) should be avoided. Moreover, this medicinal product should be used with caution in patients receiving concomitant orally administered active substances with a narrow therapeutic range that are primarily metabolised by CYP3A4, such as cyclosporine, tacrolimus, sirolimus, everolimus, alfentanil, diergotamine, ergotamine, fentanyl, and quinidine.

Effect of ketoconazole and rifampicin

Administration of the CYP3A4 inhibitor ketoconazole with netupitant/palonosetron capsules administered orally increased the AUC of netupitant 1.8 fold and C_{max} 1.3 fold when compared to the administration of Akynzeo alone. Co-administration with ketoconazole did not affect the pharmacokinetics of palonosetron.
Administration of the CYP3A4 inducer rifampicin with Akynzeo administered orally alone decreased the AUC of netupitant 5.2 fold and C_{max} 2.6 fold. Co-administration of rifampicin did not affect the pharmacokinetics of palonosetron. Consequently, concomitant administration with strong CYP3A4 inhibitors (e.g., ketoconazole) should be approached with caution and concomitant administration with strong CYP3A4 inducers (e.g. rifampicin) should be avoided.

Additional interactions

Fosnetupitant/palonosetron powder for concentrate for solution for infusion is unlikely to interact with medicinal products which are P-gp substrates. Netupitant is not a substrate for P-gp. When netupitant was administered on Day 8 of a 12-day regimen of digoxin, no changes in digoxin pharmacokinetics were observed.
Inhibition of the efflux transporter BCRP by fosenetupitant netupitant and its metabolites is unlikely and, if it occurs, of scarce clinical relevance.
In vitro data shows that fosnetupitant inhibits UGT2B7 / UGT2B15 and netupitant inhibits UGT2B7, the magnitude of such an effect in the clinical setting is not established. Caution is therefore recommended when netupitant and fosnetupitant is combined with an oral substrate of this enzyme (e.g. zidovudine, valproic acid, morphine).
In vitro data suggests that netupitant inhibits the efflux of transporter BCRP. The clinical relevance of this effect is not established.
In vitro data show that netupitant is a P-gp inhibitor. In a study performed in healthy volunteers, netupitant does not affect the exposure of digoxin, a P-gp substrate, whereas it increases its C_{max} by 1.09 fold [90%CI 0.9-1.31]. It is not excluded that this effect may be more marked, and then clinically relevant, in cancer patients, notably those having abnormal renal function. Therefore, caution is recommended when netupitant is combined with digoxin or with other P-gp substrates such as dabigatran, or colchicine.

Pharmacodynamic interactions

Akynzeo contains a 5-HT_3 receptor antagonist, palonosetron that may increase QT interval prolongation. Therefore, caution should be exercised in concomitant use with medicinal products that increase the QT interval, including but not limited to: levofloxacine, amytriptyline, alfuzosin, azythromicin, arsenic trioxide (see section 4.4).
Furthermore, caution is advised in case of fosnetupitant/palonosetron concomitantly with medicinal products known to induce hypokalaemia, such as ampicillin, albuterol, terbutaline, furosemide, thiazides, or medicinal products known to induce bradycardia, such as beta blockers, verapamil, diltiazem, digitalis, and antiarrhythmics. .

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception in females

Women of childbearing potential should not be pregnant or become pregnant while on treatment with fosnetupitant/ palonosetron powder for concentrate for solution for infusion. A pregnancy test should be performed on all pre-menopausal women prior to treatment. Women of childbearing potential must

use effective contraception during therapy and up to one month after treatment with this medicinal product.

Pregnancy

Fosnetupitant
There are no data about the use of fosnetupitant or netupitant in pregnant women. Studies in animals have shown reproductive toxicity including teratogenic effects in rabbit without safety margin (see section 5.3).

Palonosetron
There are no data about the use of palonosetron in pregnant women. Animal data do not indicate direct or indirect harmful effects of palonosetron with the respect to reproductive toxicity (see section 5.3).

Akynzeo is contraindicated during pregnancy (see section 4.3).

Breast-feeding

It is unknown whether palonosetron or netupitant are excreted in human milk. A risk to the newborns/infants cannot be excluded. Akynzeo should not be used during breast-feeding. Breast-feeding should be discontinued during treatment with this medicinal product and for 1 month after the last dose.

Fertility

Fosnetupitant
No effect on fertility has been observed in animal studies.

Palonosetron
Degeneration of seminiferous epithelium has been observed in rat study (see section 5.3).

4.7 Effects on ability to drive and use machines

Akynzeo has moderate influence on the ability to drive and use machines. Since it may induce dizziness, somnolence or fatigue, patients should be cautioned not to drive or use machines if such symptoms occur.

4.8 Undesirable effects

Summary of the safety profile

Common adverse reactions reported with Akynzeo were headache (3.6%), constipation (3.0%) and fatigue (1.2%). None of these events was serious.

Tabulated list of adverse reactions

Adverse reactions are listed below by MedDRA body system organ class and frequency.

The following convention has been used for classification of frequency:
Very common (≥1/10),
Common (≥1/100 to <1/10),
Uncommon (≥1/1000 to <1/100),
Rare (≥1/10 000 to <1/1 000),
Very rare (<1/10 000),
Not known (cannot be estimated from the available data).

Table 1: Adverse reactions

System organ class	Common	Uncommon	Rare
Infections and infestations			Cystitis
Blood and lymphatic system disorders		Neutropenia	Leukopenia
		Leucocytosis	Lymphocytosis
Metabolism and nutrition disorders		Decreased appetite	Hypokalaemia
Psychiatric disorders		Insomnia	Acute psychosis
			Mood altered
			Sleep disorder
Nervous system disorders	Headache	Dizziness	Hypoaesthesia
			Somnolence
Eye disorders			Conjunctivitis
			Vision blurred
Ear and labyrinth disorders		Vertigo	Tinnitus
Cardiac disorders		Atrioventricular block first degree	Arrhythmia
		Cardiomyopathy	Atrioventricular block second degree
		Conduction disorder	Bundle branch block left
		Tachycardia	Bundle branch block right
			Mitral valve incompetence
			Myocardial ischaemia
			Ventricular extrasystoles
Vascular disorders		Hypertension	Flushing
			Hypotension
Respiratory, thoracic and mediastinal disorders		Hiccups	
Gastrointestinal disorders	Constipation	Abdominal distension	Dry mouth
		Abdominal pain	Dysphagia
		Diarrhoea	Eructation
		Dyspepsia	Haemorrhoids
		Flatulence	Tongue coated
		Nausea	Vomiting
Skin and subcutaneous tissue disorders		Alopecia	Erythema
		Urticaria	Pruritus
			Rash
Musculoskeletal and connective tissue disorders			Back pain
			Pain in extremities
General disorders and administration site conditions	Fatigue	Asthenia	Feeling hot
			Non-cardiac chest pain
			Product taste abnormal
Investigations		Liver transaminases increased	Blood bilirubin increased
		Blood alkaline phosphatase increased	Blood creatine phosphokinase increased
		Blood creatinine increased	Blood creatine Phosphokinase MB increased

		Electrocardiogram QT prolonged	Blood urea increased
			Electrocardiogram ST segment depression
			Electrocardiogram ST-T segment abnormal
			Myoglobin blood increased
			Neutrophil count increased
			Troponin increased

Post-marketing data indicates that the adverse reactions profile is generally similar to that seen in clinical trials.

Description of selected adverse reactions

Netupitant:
No common adverse reactions are attributable to netupitant, the new component of the fixed combination.

Palonosetron:
Cases of constipation with faecal impaction requiring hospitalisation have been reported in association with palonosetron 0.75 mg.

In addition, eye swelling, dyspnoea and myalgia have been reported as adverse reactions with oral palonosetron but not observed during the development of netupitant and palonosetron hydrochloride combination. All these reactions were uncommon.

Very rare cases of anaphylaxis, anaphylactic/anaphylactoid reactions and shock have been reported from the post-marketing use of intravenous palonosetron. The signs may include hives, itch, angioedema, low blood pressure, throat tightness, chest tightness, dyspnoea, loss of consciousness.

Cases of serotonin syndrome have reported with palonosetron alone. The signs may include tremor, agitation, sweating, myoclonic movements, hypertonia and fever.

The safety profile of Akynzeo 235 mg/0.25 mg powder for concentrate for solution for infusion was similar to that seen with Akynzeo 300 mg/0.5 mg hard capsules.

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

Based on the experience with healthy subjects exposed to oral netupitant 600 mg in combination with palonosetron 1.50 mg the potential acute symptoms of overdose are headache, dizziness, constipation, anxiety, palpitations, euphoric mood and pain in the legs. In case of overdose, the medicinal product should be discontinued and general supportive treatment and monitoring should be provided. Because of the antiemetic activity of netupitant and palonosetron, emesis induced by a medicinal product may not be effective. Dialysis studies have not been performed. However, due to the large volume of distribution of palonosetron and netupitant, dialysis is unlikely to be an effective treatment for overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiemetics and antinauseants, serotonin (5-HT_3) antagonists; ATC code: A04AA55

Mechanism of action

Netupitant is a selective antagonist of human substance P/neurokinin 1 (NK_1) receptors.

Fosnetupitant is the prodrug of netupitant and when administered intravenously is converted rapidly to netupitant (see section 5.2).

Palonosetron is a 5-HT_3 receptor antagonist with a strong binding affinity for this receptor and little or no affinity for other receptors. Chemotherapeutic substances produce nausea and vomiting by stimulating the release of serotonin from the enterochromaffin cells of the small intestine. Serotonin then activates 5-HT_3 receptors located on vagal afferents to initiate the vomiting reflex.

Delayed emesis has been associated with the activation of tachykinin family neurokinin 1 (NK_1) receptors (broadly distributed in the central and peripheral nervous systems) by substance P. As shown in *in vitro* and *in vivo* studies, netupitant inhibits substance P mediated responses.

Netupitant was shown to cross the blood brain barrier with a NK_1 receptor occupancy of 92.5%, 86.5%, 85.0%, 78.0%, and 76.0% in striatum at 6, 24, 48, 72, and 96 hours, respectively, after administration of 300 mg netupitant.

Clinical efficacy and safety

Oral administration of Akynzeo in combination with dexamethasone has been shown to prevent acute and delayed nausea and vomiting associated with highly and moderately emetogenic cancer chemotherapy in two separate pivotal studies.

Highly Emetogenic Chemotherapy (HEC) study
In a multicenter, randomized, parallel, double-blind, controlled clinical study of 694 patients, the efficacy and safety of single doses of oral netupitant in combination with oral palonosetron was compared with a single oral dose of palonosetron in cancer patients receiving a chemotherapy regimen that included cisplatin (median dose = 75 mg/m^2). The efficacy of Akynzeo was assessed in 135 patients who received a single oral dose (netupitant 300 mg and palonosetron 0.5 mg) and 136 patients who received oral palonosetron 0.5 mg alone.

Treatment regimens for the Akynzeo and the palonosetron 0.5 mg arms are displayed in Table 2 below.

Table 2: Oral antiemetic treatment regimen — HEC study

Treatment regimen	Day 1	Days 2 to 4
Akynzeo	Akynzeo (Netupitant 300 mg + Palonosetron 0.5 mg) Dexamethasone 12 mg	Dexamethasone 8 mg once a day
Palonosetron	Palonosetron 0.5 mg Dexamethasone 20 mg	Dexamethasone 8 mg twice a day

The primary efficacy endpoint was complete response (CR) rate (defined as no emetic episodes, no rescue medication) within 120 hours (overall phase) after the start of the highly emetogenic chemotherapy administration.
A summary of the key results from this study is shown in Table 3 below.

Table 3: Proportion of patients receiving cisplatin chemotherapy responding by treatment group and phase

	Akynzeo N=135 %	Palonosetron 0.5 mg N=136 %	p-value
Primary endpoint			
Complete response			
Overall phase[§]	89.6	76.5	0.004
Major secondary endpoints			
Complete response			
Acute phase[‡]	98.5	89.7	0.007
Delayed phase[†]	90.4	80.1	0.018
No emesis			
Acute phase	98.5	89.7	0.007
Delayed phase	91.9	80.1	0.006
Overall phase	91.1	76.5	0.001
No significant nausea			
Acute phase	98.5	93.4	0.050
Delayed phase	90.4	80.9	0.004
Overall phase	89.6	79.4	0.021

[‡]Acute phase: 0 to 24 hours post-cisplatin treatment.
[†]Delayed phase: 25 to 120 hours post-cisplatin treatment.
[§]Overall: 0 to 120 hours post-cisplatin treatment.

Moderately Emetogenic Chemotherapy (MEC) study
In a multicenter, randomized, parallel, double-blind, active-controlled, superiority study, the efficacy and safety of a single oral dose of Akynzeo was compared with a single oral dose of palonosetron 0.5 mg in cancer patients scheduled to receive the first cycle of an anthracycline and cyclophosphamide regimen for the treatment of a solid malignant tumour. At the time of the study, anthracycline-cyclophosphamide containing chemotherapy regimens were considered to be moderately emetogenic. Recent guidance has updated these regimens to highly emetogenic.
All patients received a single oral dose of dexamethasone.

Table 4: Oral antiemetic treatment regimen – MEC study

Treatment regimen	**Day 1**	**Days 2 to 3**
Akynzeo	Akynzeo (Netupitant 300 mg + Palonosetron 0.5 mg) Dexamethasone 12 mg	No antiemetic treatment
Palonosetron	Palonosetron 0.5 mg Dexamethasone 20 mg	No antiemetic treatment

After completion of cycle 1, patients had the option to participate in a multiple-cycle extension, receiving the same treatment as assigned in cycle 1. There was no pre-specified limit of the number of repeat consecutive cycles for any patient. A total of 1450 patients (Akynzeo n=725; Palonosetron n=725) received study medication. Of these, 1438 patients (98.8%) completed cycle 1 and 1286 patients (88.4%) continued treatment in the multiple-cycle extension. A total of 907 patients (62.3%) completed the multiple-cycle extension up to a maximum of eight treatment cycles.

A total of 724 patients (99.9%) were treated with cyclophosphamide. All patients were additionally treated with either doxorubicin (68.0%) or epirubicin (32.0%).

The primary efficacy endpoint was the CR rate in the delayed phase, 25-120 hours after the start of the chemotherapy administration.

A summary of the key results from this study is shown in the table 5 below.

Table 5: Proportion of patients receiving anthracycline and cyclophosphamide chemotherapy responding by treatment group and phase – cycle 1

	Akynzeo N=724 %	Palonosetron 0.5 mg N=725 %	p-value*
Primary endpoint			
Complete response			
Delayed phase[†]	76.9	69.5	0.001
Major secondary endpoints			
Complete response			
Acute phase[‡]	88.4	85.0	0.047
Overall phase[§]	74.3	66.6	0.001
No emesis			
Acute phase	90.9	87.3	0.025
Delayed phase	81.8	75.6	0.004
Overall phase	79.8	72.1	<0.001
No significant nausea			
Acute phase	87.3	87.9	N.S.
Delayed phase	76.9	71.3	0.014
Overall phase	74.6	69.1	0.020

* p-value from Cochran-Mantel-Haenszel test, stratified by age class and region.
[‡]Acute phase: 0 to 24 hours after anthracycline and cyclophosphamide regimen
[†]Delayed phase: 25 to 120 hours after anthracycline and cyclophosphamide regimen
[§]Overall: 0 to 120 hours after anthracycline and cyclophosphamide regimen

Patients continued into the Multiple-Cycle extension for up to 7 additional cycles of chemotherapy. Antiemetic activity of Akynzeo was maintained throughout repeat cycles for those patients continuing in each of the multiple cycles.
The impact of nausea and vomiting on patients' daily lives was assessed using the Functional Living Index–Emesis (FLIE). The proportion of patients with Overall no impact on daily life was 6.3% higher (p value =0.005) in the Akynzeo group (78.5%) than in the palonosetron group (72.1%).

Multiple-cycle safety study in patients receiving either Highly Emetogenic Chemotherapy or Moderately Emetogenic Chemotherapy
In a separate study, a total of 413 patients undergoing initial and repeat cycles of chemotherapy (including carboplatin, cisplatin, oxaliplatin, and doxorubicin regimens), were randomized to receive either Akynzeo (n=309) or aprepitant and palonosetron (n=104). Safety and efficacy were maintained throughout all cycles.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Akynzeo in one or more subsets of the paediatric population in prevention of chemotherapy-induced nausea and vomiting, as per PIP decision in the granted indication. See section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

Absorption

Netupitant
Absolute netupitant bioavailability data are not available in humans; based on data from two studies with intravenous netupitant, the bioavailability in humans is estimated to be greater than 60%.
In single dose oral studies, netupitant was measurable in plasma between 15 minutes and 3 hours after dosing. Plasma concentrations followed a first order absorption process and reached C_{max} in approximately 5 hours. There was a supra-proportional increase in C_{max} and AUC parameters for doses from 10 mg to 300 mg.
In 82 healthy subjects given a single oral dose of netupitant 300 mg, maximum plasma netupitant concentration (C_{max}) was 486 ±268 ng/mL (mean ± SD) and median time to maximum concentration (T_{max}) was 5.25 hours, the AUC was 15032 ± 6858 h.ng/mL. In a pooled analysis, females had a higher netupitant exposure compared to males; there was a 1.31-fold increase in C_{max}, a 1.02 fold increase for AUC and a 1.36 fold increase in half-life.
Netupitant $AUC_{0-\infty}$ and C_{max} increased by 1.1 fold and 1.2 fold, respectively, after a high fat meal.

Fosnetupitant
After single dose administration of Akynzeo, administered as a 30-minute infusion to healthy subjects and cancer patients, fosnetupitant achieved C_{max} at the end of the infusion with an apparent terminal half-life less than 1 hour. Within 30 minutes of completion of the infusion, the concentration of fosnetupitant decreased to less than 1% of the C_{max}. The pharmacokinetic parameters of netupitant and palonosetron were similar to those observed after Akynzeo 300 mg/0.5 mg hard capsules.

Table 6: PK Parameters (mean and CV%) After Single Dose Administration Akynzeo Powder for Concentrate for Solution for Infusion in Healthy Volunteers (HVs) and Cancer Patients

		Fosnetupitant	Netupitant	Palonosetron[2]
C_{max} (ng/mL)	HVs	6431 (14)	841 (21)	2.1 (61)
	Patients	3478 (45)	590 (28)	0.8 (35)
t_{max}[1] (h)	HVs	0.5 (0.25 – 0.5)	0.5 (0.5 – 0.4)	0.55
	Patients	0.5 (0.5 – 0.6)	0.6 (0.5 – 4)	0.6 (0.5 – 6)
AUC (ng*h/mL)	HVs	2938 (12)	13854 (21)	35 (33)
	Patients	1401 (46)	15588 (32)	36 (30)
$t_{1/2}$ (h)	HVs	0.96 (57)	36.1 (19)	43 (32)
	Patients	0.75 (54)	144 (50)	58 (47)

[1] median (min-max); [2] IV bolus in HVs

Fosnetupitant C_{max} and AUC were lower in patients than in healthy subjects, although the systemic exposures to netupitant were comparable.

In healthy subjects, there was a dose-proportional increase in the systemic exposure of fosnetupitant with the dose increase of fosnetupitant from 17.6 to 353 mg

Palonosetron
Following oral administration, palonosetron is well absorbed with its absolute bioavailability reaching 97%. After single oral doses using buffered solution mean maximum palonosetron concentrations (C_{max}) and area under the concentration-time curve ($AUC_{0-\infty}$) were dose proportional over the dose range of 3.0 to 80 mcg/kg in healthy subjects.
In 36 healthy male and female subjects given a single oral dose of 0.5 mg palonosetron, maximum plasma concentration (C_{max}) was 0.81 ± 1.66 ng/mL (mean ± SD) and time to maximum concentration (T_{max}) was 5.1 ± 1.7 hours. In female subjects (n=18), the mean AUC was 35% higher and the mean

C_{max} was 26% higher than in male subjects (n=18). In 12 cancer patients given a single oral dose of palonosetron 0.5 mg one hour prior to chemotherapy, C_{max} was 0.93 ± 0.34 ng/mL and T_{max} was 5.1 ± 5.9 hours. The AUC was 30% higher in cancer patients than in healthy subjects. A high fat meal did not affect the C_{max} and AUC of oral palonosetron.

Distribution

Netupitant
After a single oral 300 mg dose administration in cancer patients, netupitant disposition was characterised by a two compartment model with an estimated median systemic clearance of 20.5 L/h and a large distribution volume in the central compartment (486 L). Human plasma protein binding of netupitant and its two major metabolites M1 and M3 is > 99% at concentrations ranging from 10 to 1500 ng/mL. The third major metabolite, M2, is > 97% bound to plasma proteins.

Fosnetupitant
The mean ± SD volume of distribution (Vz) of fosnetupitant in healthy subjects and in patients was 124 ± 76 L and 296 ±535 L, respectively. The human plasma protein binding of fosnetupitant was 92% at 1 micromolar and 95% at 10 micromolar. The free fraction was in the range 5 to 8%.

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

Biotransformation

Netupitant
Three metabolites have been detected in human plasma at netupitant oral doses of 30 mg and higher (the desmethyl derivative, M1; the N-oxide derivative, M2; the OH-methyl derivative, M3). *In vitro* metabolism studies have suggested that CYP3A4 and, to a lesser extent, CYP2D6 and CYP2C9 are involved in the metabolism of netupitant. After administration of a single oral dose of 300 mg netupitant, mean plasma netupitant/plasma radioactivity ratios ranged from 0.13 to 0.49 over 96 h post-dose. The ratios were time dependent with values decreasing gradually beyond 24 h post-dose, indicating that netupitant is being rapidly metabolised. Mean C_{max} was approximately 11%, 47% and 16% of the parent for M1, M2 and M3 respectively; M2 had the lowest AUC relative to the parent (14%) whereas M1 and M3 AUC were approximately 29% and 33% of the parent, respectively. M1, M2 and M3 metabolites were all shown to be pharmacologically active in an animal pharmacodynamic model, where M3 was most potent and M2 least active.

Fosnetupitant
Fosnetupitant is rapidly converted *in vivo* to netupitant by metabolic hydrolysis. In patients receiving Akynzeo 235 mg/0.25 mg powder concentrate for solution for infusion intravenously, netupitant exposure was 17-fold fosnetupitant exposure, as determined by their AUC ratio. Netupitant metabolites M1, M2 and M3 were rapidly generated from the released netupitant. In patients, metabolite M1, M2 and M3 exposures were 32%, 21% and 28% of netupitant exposure, as determined by their AUC ratio. The median t_{max} for M1, M2, and M3 were 12, 2 and 12 hours, respectively.

Palonosetron
Palonosetron is eliminated by multiple routes with approximately 50% metabolised to form two primary metabolites: N-oxide-palonosetron and 6-S-hydroxy-palonosetron. These metabolites each have less than 1% of the 5-HT_3 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

Netupitant
Following administration of a single dose of Akynzeo, netupitant is eliminated from the body in a multi-exponential fashion, with an apparent mean elimination half-life of 88 hours in cancer patients. Renal clearance is not a significant elimination route for netupitant-related entities. The mean fraction of an oral dose of netupitant excreted unchanged in urine is less than 1%; a total of 3.95% and 70.7% of the radioactive dose was recovered in the urine and faeces, respectively.
Approximately half the radioactivity administered orally as [14C]-netupitant was recovered from urine and faeces within 120 h of dosing. Elimination via both routes was estimated to be complete by Day 29-30 post-dose.

Fosnetupitant
After intravenous Akynzeo 235 mg/0.25 mg powder concentrate for solution for infusion administration, fosnetupitant plasma concentrations declined according to a biexponential profile. Thirty minutes after the end of the infusion, the mean plasma concentration of fosnetupitant was less than 1% of $C_{max.}$

Palonosetron
Following administration of a single oral 0.75 mg dose of [14C]-palonosetron to six healthy subjects, 85% to 93% of the total radioactivity was excreted in urine, and 5% to 8% was eliminated in faeces. The amount of unchanged palonosetron excreted in the urine represented approximately 40% of the administered dose. In healthy subjects given palonosetron capsules 0.5 mg, the terminal elimination half-life (t½) of palonosetron was 37 ± 12 hours (mean ± SD), and in cancer patients, t½ was 48 ± 19 hours. After a single dose of approximately 0.75 mg intravenous palonosetron, the total body clearance of palonosetron in healthy subjects was 160 ± 35 mL/h/kg (mean ± SD) and renal clearance was 66.5± 18.2 mL/h/kg.

<u>*Special populations*</u>

<u>*Hepatic impairment*</u>

Netupitant
Maximum concentrations and total exposure of netupitant were increased in subjects with mild (n=8), moderate (n=8), and severe (n=2) hepatic impairment compared to matching healthy subjects, although there was pronounced individual variability in both hepatically-impaired and healthy subjects. Exposure to netupitant (C_{max}, AUC_{0-t} and $AUC_{0-\infty}$) compared to matching healthy subjects was 11%, 28% and 19% higher in mild and 70%, 88% and 143% higher in moderate hepatically-impaired subjects, respectively. As such, no dose adjustment is necessary for patients with mild to moderate hepatic impairment. Limited data exist in patients with severe hepatic impairment (Child Pugh score ≥9).

Palonosetron
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.

<u>*Renal impairment*</u>

Netupitant
No specific studies were performed to evaluate netupitant in patients with renal impairment. In the ADME trial, less than 5% of all netupitant-related material was excreted in urine and less than 1% of the netupitant dose was eliminated unchanged in the urine and therefore any accumulation of netupitant or metabolites after a single dose would be negligible. Furthermore, the population PK study showed no correlation between PK parameters of netupitant and markers of renal dysfunction.

Palonosetron
Mild to moderate renal impairment does not significantly affect palonosetron PK parameters. Total systemic exposure to intravenous palonosetron increased by approximately 28% in patients with

severe impairment relative to healthy subjects. In a population PK study, patients with a reduced creatinine clearance (CL_{CR}) also had a reduced palonosetron clearance, but this reduction would not result in a significant change in palonosetron exposure.

Therefore, Akynzeo can be administered without dose adjustment in patients with renal impairment.

Neither netupitant nor palonosetron have been evaluated in patients with end-stage renal disease.

5.3 Preclinical safety data

Palonosetron

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. Degeneration of seminiferous epithelium was associated with palonosetron following a one month oral repeat dose toxicity study in rats. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. Only limited data from animal studies are available regarding the placental transfer (see section 4.6). Palonosetron is not mutagenic. High doses of palonosetron (each dose causing at least 15 times the human therapeutic exposure) applied daily for two years caused an increased rate of liver tumours, endocrine neoplasms (in thyroid, pituitary, pancreas, adrenal medulla) and skin tumours in rats but not in mice. The underlying mechanisms are not fully understood, but because of the high doses employed and since the medicinal product is intended for single application in humans, these findings are not considered relevant for clinical use.

Netupitant and combination with palonosetron

Effects in non-clinical studies based on safety pharmacology and single and repeated dose toxicity were observed only at exposures considered in excess of the maximum human exposure, indicating little relevance to clinical use. Phospholipidosis (foamy macrophages) has been observed with the administration of netupitant after repeated administration in rats and dogs. The effects were reversible or partially reversible after the recovery period. The significance of these findings in humans is unknown.

Non-clinical studies indicate that netupitant and its metabolites and the combination with palonosetron only at very high concentrations may block ion channels involved in ventricular de- and re-polarisation and prolong action potential duration. Reproductive studies in animals with netupitant do not indicate direct or indirect harmful effects with respect to fertility, parturition or postnatal development. An increased incidence of positional foetal abnormalities of the limbs and paws, fused sternebrae and agenesis of accessory lung lobe were observed following daily administration of netupitant in rabbits at 10 mg/kg/day and higher during the period of organogenesis. In a pilot dose range finding study in rabbits, cleft palate, microphtalmia and aphakia were observed in four foetuses from one litter in the 30 mg/kg/day group. The relevance of these findings in humans is unknown. No data from animal studies with netupitant are available regarding placental transfer and lactation. Netupitant is not mutagenic.

Fosnetupitant

Daily intravenous administration of fosnetupitant in rats (at 3 times the human AUC for netupitant at the recommended single dose to be given with each cycle of chemotherapy) during the period of organogenesis produced delayed ossification of pubis. No effects on embryo-fetal development were observed with daily administration of up to 13 mg/kg fosnetupitant in rats (2 times the human AUC for netupitant at the recommended single dose to be given with each cycle of chemotherapy). Due to the limited systemic exposure to fosnetupitant in pregnant rats, it is not possible to provide an AUC-based comparison of fosnetupitant exposure in rats and humans. An increase in resorptions was observed with daily intravenous administration of fosnetupitant at 6 mg/kg/day and higher in rabbits

(9 times the human AUC for fosnetupitant and 0.4 times the human AUC for netupitant at the recommended single dose to be given with each cycle of chemotherapy) during the period of organogenesis. No effects were observed in rabbits at 3 mg/kg/day (5.4 times the human AUC for fosnetupitant and 0.4 times the human AUC for netupitant at the recommended single dose to be given with each cycle of chemotherapy). Daily intravenous administration of 39 mg/kg fosnetupitant in rats (3 times the AUC for netupitant at the recommended single dose to be given with each cycle of chemotherapy) during organogenesis through lactation produced lower bodyweight in offspring at birth through maturation, and delayed physical development (pinna detachment, eye opening, and preputial separation). These effects were associated with maternal toxicity (reduced weight gain and food consumption). No effects occurred in offspring or dams at 13 mg/kg/day (2 times the human AUC for netupitant at the recommended single dose to be given with each cycle of chemotherapy).

Fosnetupitant–palonosetron combination

Intravenous and Intra-arterial administration in rabbits: for the clinical signs very slight to mild erythema were observed. No changes were noted at microscopic examination.
Paravenous administration (a non-intended clinical route/misapplication) in rabbits: for the clinical signs very slight to mild erythema and very slight oedema were observed. At microscopic examination chronic inflammation (from mild to moderate), epidermal hyperplasia (from minimal to mild) of dermis were reported.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Disodium edetate (E386)
Sodium hydroxide (E524) (for pH adjustment)
Hydrochloric acid (E507) (1M for pH adjustment)

6.2 Incompatibilities

Akynzeo powder for concentrate for solution for infusion is incompatible with any solutions containing divalent cations (e.g., Ca^{2+}, Mg^{2+}), including Hartman's and lactated Ringer's solutions.

Akynzeo powder for concentrate for solution for infusion should not be infused simultaneously or mixed with other intravenous substances, additives or medicinal products unless compatibility has been demonstrated. If the same intravenous line is used for sequential infusion of several different medicinal products, the line should be flushed before and after infusion of Akynzeo with sodium chloride 9 mg/ml (0.9%) solution for injection.

6.3 Shelf life

5 years.

Store the reconstituted and diluted solution below 25°C.

The product should be diluted immediately after reconstitution. Chemical, physical and microbiological in-use stability after reconstitution and dilution has been demonstrated for 24 hours at 25°C.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Keep the vial in the outer carton in order to protect from light.
For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Single-dose 50 mL glass vials with 20 mm rubber stoppers and 20 mm aluminium cap seals.
Pack of 1 vial.

6.6 Special precautions for disposal and other handling

Akynzeo must be reconstituted and then diluted prior to administration.

Preparation of Akynzeo

Step 1	Aseptically inject 20 mL 5% glucose injection or sodium chloride 9 mg/ml (0.9%) solution for injection, into the vial. Ensure the solvent is added to the vial along the vial wall and not jetted in order to prevent foaming. Swirl the vial gently for 3 minutes. The powder should be dissolved before the solution is diluted in the infusion bag.
Step 2	Aseptically prepare an infusion vial or bag filled with 30 mL of 5% glucose injection, or sodium chloride 9 mg/ml (0.9%) solution for injection.
Step 3	Dilution should occur immediately after reconstitution (according to Step 1). Aseptically withdraw the entire volume of reconstituted solution from the AKYNZEO vial and transfer it into the infusion vial or bag containing 30 mL of 5% glucose injection or sodium chloride 9 mg/ml (0.9%) solution for injection to yield a total volume of 50 mL.
Step 4	Gently invert the vial or bag until complete dissolution.
Step 5	Before administration, inspect the final diluted solution for particulate matter and discolouration. Discard the vial or bag if particulates and/or discolouration are observed.

Akynzeo must not be reconstituted or mixed with solutions for which physical and chemical compatibility has not been established (see section 6.2).

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

7. MARKETING AUTHORISATION HOLDER

Helsinn Birex Pharmaceuticals Ltd.
Damastown
Mulhuddart
Dublin 15
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1001/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27 May 2015
Date of latest renewal: 9 January 2020

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Akynzeo 235 mg/0.25 mg concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of 20 ml contains 235 mg of fosnetupitant (as chloride hydrochloride), which corresponds to 197.5 mg of netupitant, and 0.25 mg of palonosetron (as hydrochloride).
Each ml of concentrate for solution contains 11.75 mg fosnetupitant, which corresponds to 9.87 mg of netupitant, and 0.0125 mg palonosetron

After dilution 1 ml of solution contains 4.7 mg fosnetupitant, which corresponds to 3.95 mg of netupitant, and 0.005 mg palonosetron.

Excipients with known effect

Each vial contains approximately 24.4 mg of sodium.
If diluted with sodium chloride 9 mg/ml (0.9%) solution for injection, the final solution contains approximately 202 mg of sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Clear, colourless to slightly yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Akynzeo is indicated in adults for the:
- Prevention of acute and delayed nausea and vomiting associated with highly emetogenic cisplatin-based cancer chemotherapy.
- Prevention of acute and delayed nausea and vomiting associated with moderately emetogenic cancer chemotherapy.

4.2 Posology and method of administration

Posology

The recommended dose is 235 mg/0.25 mg (the content of one vial of concentrate, diluted) administered as an infusion over 30 minutes, initiated approximately 30 minutes prior to the start of each chemotherapy cycle (see section 6.6).
At the end of the infusion, the infusion line should be flushed with the same carrier solution to ensure complete medicinal product administration.

The recommended oral dexamethasone dose should be reduced by approximately 50 % when co-administered with fosnetupitant and palonosetron hydrochloride combination (see section 4.5 and clinical studies administration schedule in section 5.1).

Special populations

Elderly people

No dose adjustment is necessary for elderly patients. Caution should be exercised when using this medicinal product in patients over 75 years, due to the long half-life of the active substances and the limited experience in this population.

Renal impairment

Dose adjustment is not considered necessary in patients with mild to severe renal impairment. Renal excretion for netupitant is negligible. Mild to moderate renal impairment does not significantly affect palonosetron pharmacokinetic parameters. Total systemic exposure to intravenous palonosetron increased by approximately 28% in severe renal impairment relative to healthy subjects. The pharmacokinetics of palonosetron or netupitant have not been studied in subjects with end-stage renal disease requiring hemodialysis and no data on the effectiveness or safety of fosnetupitant and palonosetron hydrochloride combination in these patients are available. Therefore, the use in these patients should be avoided.

Hepatic impairment

No dose adjustment is necessary for patients with mild or moderate hepatic impairment (Child-Pugh score 5-8). Limited data exist in patients with severe hepatic impairment (Child Pugh score ≥ 9). As use in patients with severe hepatic impairment may be associated with increased exposure of netupitant, this medicinal product should be used with caution in these patients (see sections 4.4 and 5.2).

Paediatric population

The safety and efficacy of Akynzeo in children aged 1 month to less than 18 years have not yet been established. No data are available.

Method of administration

This medicinal product should be administered intravenously. Intravenous administration occurs preferably through a running intravenous infusion over 30 minutes (see section 6.6).

For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

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

Pregnancy (see section 4.6).

4.4 Special warnings and precautions for use

Constipation

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 (see section 4.8).

Serotonin syndrome

There have been reports of serotonin syndrome with the use of 5-HT_3 antagonists either alone or in combination with other serotonergic medicinal products (including selective serotonin reuptake inhibitors (SSRIs) and serotonin noradrenaline reuptake inhibitors (SNRIs). Appropriate observation of patients for serotonin syndrome-like symptoms is advised (see section 4.8).

QT Prolongation

An ECG study was conducted in adult male and female healthy volunteers with oral netupitant either 200 mg or 600 mg administered in combination with oral palonosetron 0.5 mg or 1.5 mg, respectively. The study demonstrated no clinically important effects on ECG parameters: the largest point estimate of the placebo and baseline corrected QTc interval was 7.0 ms (one-sided upper 95% confidence limit 8.8 ms), observed 16 hours after the administration of supratherapeutic doses (600 mg netupitant and 1.5 mg palonosetron). The upper 95% confidence limit of the point estimates of placebo and baseline corrected QTcI was constantly within 10 ms at all time points over 2 days after study administration of the medicinal product.

However, since netupitant and palonosetron hydrochloride combination contains a 5-HT_3 receptor antagonist, caution should be exercised in concomitant use with medicinal products that increase the QT interval or 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, bradyarrhythmia, conduction disturbances and in patients taking anti-arrhythmic medicinal products or other medicinal products that lead to QT prolongation or electrolyte abnormalities. Hypokalaemia and hypomagnesaemia should be corrected prior to administration.

This medicinal product should not be used to prevent nausea and vomiting in the days following chemotherapy if not associated with another chemotherapy administration.

It should not be used to treat nausea and vomiting following chemotherapy.

Caution should be exercised in patients with severe hepatic impairment since limited data are available in these patients.

This medicinal product should be used with caution in patients receiving concomitant orally administered active substances that are metabolised primarily through CYP3A4 and with a narrow therapeutic range (see section 4.5).

Chemotherapeutic agents that are substrates for CYP3A4

Netupitant is a moderate inhibitor of CYP3A4 and can increase the exposure of chemotherapeutic agents that are substrates for CYP3A4, e.g. docetaxel (see section 4.5). Therefore, patients should be monitored for increased toxicity of chemotherapeutic agents that are substrates for CYP3A4, including irinotecan. Furthermore, netupitant may also affect the efficacy of chemotherapeutic agents that need activation by CYP3A4 metabolism.

Excipients

This medicinal product contains approximately 24.4 mg of sodium per vial, equivalent to 1.22% of the WHO recommended maximum daily intake of 2 g sodium for an adult.
If diluted with sodium chloride 9 mg/ml (0.9%) solution for injection, the final solution contains approximately 202 mg of sodium per dose, equivalent to 10.1% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interactions

When administered intravenously fosnetupitant is rapidly converted to netupitant.
Interactions with other medicinal products following administration of intravenous fosnetupitant are likely to occur with active substances that interact with oral netupitant. The following information was derived from studies conducted with oral netupitant and studies conducted with intravenous fosnetupitant.

In humans, netupitant is eliminated mainly by hepatic metabolism mediated by CYP3A4 with a marginal renal excretion. At a dose of 300 mg in humans, netupitant is a substrate and moderate inhibitor of CYP3A4. Palonosetron is eliminated from the body through both renal excretion and metabolic pathways, with the latter mediated via multiple CYP enzymes. 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.

Interaction between oral netupitant and oral palonosetron

No clinically relevant pharmacokinetic interactions have been observed between oral netupitant and oral palonosetron.

Interaction with CYP3A4 substrates

Dexamethasone
Co-administration of a single oral dose of 300 mg netupitant or a single intravenous dose of 235 mg fosnetupitant with a dexamethasone regimen (20 mg on Day 1, followed by 8 mg twice daily from Day 2 to Day 4) significantly increased the exposure to dexamethasone in a time and dose dependent manner. The $AUC_{84-\infty}$ (Day 4) of dexamethasone increased 2.4-fold with co-administration of 300 mg netupitant or 235 mg fosnetupitant. The pharmacokinetic profile of netupitant was unchanged when administered in combination with dexamethasone.
As such, the oral dexamethasone dose should be reduced by approximately 50% when co-administered with fosnetupitant and palonosetron hydrochloride combination (see section 4.2).

Chemotherapeutic medicinal products (docetaxel, etoposide, cyclophosphamide)
Exposure to docetaxel and etoposide was increased 37% and 21%, respectively, when co-administered with netupitant/palonosetron capsules. No consistent effect was seen with cyclophosphamide after netupitant co-administration.

Oral contraceptives
Netupitant/palonosetron capsules, when given with a single oral dose of 60 mcg ethinylestradiol and 300 mcg levonorgestrel had no significant effect on the AUC of ethinylestradiol and increased the AUC of levonorgestrel by 1.4-fold; clinical effects on the efficacy of hormonal contraception are unlikely. No relevant changes of netupitant and palonosetron pharmacokinetics were observed.

Erythromycin and midazolam
Exposure to erythromycin and midazolam was increased approximately 1.3 and 2.4 fold, respectively, when each was co-administered with netupitant administered orally. These effects were not considered clinically important. The pharmacokinetic profile of netupitant was unaffected by the concomitant administration of either midazolam or erythromycin. The potential effects of increased plasma concentrations of midazolam or other benzodiazepines metabolised via CYP3A4 (alprazolam, triazolam) should be considered when coadministering these active substances with netupitant and palonosetron hydrochloride combination.

Serotonergic medicinal products (e.g. SSRIs and SNRIs)

There have been reports of serotonin syndrome following concomitant use of 5-HT_3 antagonists and other serotonergic medicinal products (including SSRIs such as fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram or escitalopram and SNRIs such as venlafaxine or duloxetine) (see section 4.4).

Effect of other medicinal products on the pharmacokinetics of Akynzeo

Netupitant is mainly metabolised by CYP3A4; therefore, co-administration with medicinal products that inhibit or induce CYP3A4 activity may influence plasma concentrations of netupitant. Consequently, concomitant administration with strong CYP3A4 inhibitors (e.g., ketoconazole) should

be approached with caution and concomitant administration with strong CYP3A4 inducers (e.g., rifampicin) should be avoided. Moreover, this medicinal product should be used with caution in patients receiving concomitant orally administered active substances with a narrow therapeutic range that are primarily metabolised by CYP3A4, such as cyclosporine, tacrolimus, sirolimus, everolimus, alfentanil, diergotamine, ergotamine, fentanyl, and quinidine.

Effect of ketoconazole and rifampicin

Administration of the CYP3A4 inhibitor ketoconazole with netupitant/palonosetron capsules administered orally increased the AUC of netupitant 1.8 fold and C_{max} 1.3 fold when compared to the administration of Akynzeo alone. Co-administration with ketoconazole did not affect the pharmacokinetics of palonosetron.
Administration of the CYP3A4 inducer rifampicin with Akynzeo administered orally alone decreased the AUC of netupitant 5.2 fold and C_{max} 2.6 fold. Co-administration of rifampicin did not affect the pharmacokinetics of palonosetron. Consequently, concomitant administration with strong CYP3A4 inhibitors (e.g., ketoconazole) should be approached with caution and concomitant administration with strong CYP3A4 inducers (e.g. rifampicin) should be avoided.

Additional interactions
Fosnetupitant/palonosetron concentrate for solution for infusion is unlikely to interact with medicinal products which are P-gp substrates. Netupitant is not a substrate for P-gp. When netupitant was administered on Day 8 of a 12-day regimen of digoxin, no changes in digoxin pharmacokinetics were observed.
Inhibition of the efflux transporter BCRP by fosenetupitant, netupitant and its metabolites is unlikely and, if it occurs, of scarce clinical relevance.
In vitro data shows that fosnetupitant inhibits UGT2B7 / UGT2B15 and netupitant inhibits UGT2B7, the magnitude of such an effect in the clinical setting is not established. Caution is therefore recommended when netupitant and fosnetupitant is combined with an oral substrate of this enzyme (e.g. zidovudine, valproic acid, morphine).
In vitro data suggests that netupitant inhibits the efflux of transporter BCRP. The clinical relevance of this effect is not established.
In vitro data show that netupitant is a P-gp inhibitor. In a study performed in healthy volunteers, netupitant does not affect the exposure of digoxin, a P-gp substrate, whereas it increases its C_{max} by 1.09 fold [90%CI 0.9-1.31]. It is not excluded that this effect may be more marked, and then clinically relevant, in cancer patients, notably those having abnormal renal function. Therefore, caution is recommended when netupitant is combined with digoxin or with other P-gp substrates such as dabigatran, or colchicine.

Pharmacodynamic interactions

Akynzeo contains a 5-HT_3 receptor antagonist, palonosetron that may increase QT interval prolongation. Therefore, caution should be exercised in concomitant use with medicinal products that increase the QT interval, including but not limited to: levofloxacine, amytriptyline, alfuzosin, azythromicin, arsenic trioxide (see section 4.4).
Furthermore, caution is advised in case of fosnetupitant/palonosetron concomitantly with medicinal products known to induce hypokalaemia, such as ampicillin, albuterol, terbutaline, furosemide, thiazides, or medicinal products known to induce bradycardia, such as beta blockers, verapamil, diltiazem, digitalis and antiarrhythmics.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception in females

Women of childbearing potential should not be pregnant or become pregnant while on treatment with fosnetupitant/ palonosetron concentrate for solution for infusion. A pregnancy test should be performed on all pre-menopausal women prior to treatment. Women of childbearing potential must

use effective contraception during therapy and up to one month after treatment with this medicinal product.

Pregnancy

Fosnetupitant
There are no data about the use of fosnetupitant or netupitant in pregnant women. Studies in animals have shown reproductive toxicity including teratogenic effects in rabbit without safety margin (see section 5.3).

Palonosetron
There are no data about the use of palonosetron in pregnant women. Animal data do not indicate direct or indirect harmful effects of palonosetron with the respect to reproductive toxicity (see section 5.3).

Akynzeo is contraindicated during pregnancy (see section 4.3).

Breast-feeding

It is unknown whether palonosetron or netupitant are excreted in human milk. A risk to the newborns/infants cannot be excluded. Akynzeo should not be used during breast-feeding. Breast-feeding should be discontinued during treatment with this medicinal product and for 1 month after the last dose.

Fertility

Fosnetupitant
No effect on fertility has been observed in animal studies.

Palonosetron
Degeneration of seminiferous epithelium has been observed in rat study (see section 5.3).

4.7 Effects on ability to drive and use machines

Akynzeo has moderate influence on the ability to drive and use machines. Since it may induce dizziness, somnolence or fatigue, patients should be cautioned not to drive or use machines if such symptoms occur.

4.8 Undesirable effects

Summary of the safety profile

Common adverse reactions reported with Akynzeo were headache (3.6%), constipation (3.0%) and fatigue (1.2%). None of these events was serious.

Tabulated list of adverse reactions

Adverse reactions are listed below by MedDRA body system organ class and frequency.

The following convention has been used for classification of frequency:
Very common (≥1/10),
Common (≥1/100 to <1/10),
Uncommon (≥1/1 000 to <1/100),
Rare (≥1/10 000 to <1/1 000),
Very rare (<1/10 000),
Not known (cannot be estimated from the available data).

Table 1: Adverse reactions

System organ class	Common	Uncommon	Rare
Infections and infestations			Cystitis
Blood and lymphatic system disorders		Neutropenia	Leukopenia
		Leucocytosis	Lymphocytosis
Metabolism and nutrition disorders		Decreased appetite	Hypokalaemia
Psychiatric disorders		Insomnia	Acute psychosis
			Mood altered
			Sleep disorder
Nervous system disorders	Headache	Dizziness	Hypoaesthesia
			Somnolence
Eye disorders			Conjunctivitis
			Vision blurred
Ear and labyrinth disorders		Vertigo	Tinnitus
Cardiac disorders		Atrioventricular block first degree	Arrhythmia
		Cardiomyopathy	Atrioventricular block second degree
		Conduction disorder	Bundle branch block left
		Tachycardia	Bundle branch block right
			Mitral valve incompetence
			Myocardial ischaemia
			Ventricular extrasystoles
Vascular disorders		Hypertension	Flushing
			Hypotension
Respiratory, thoracic and mediastinal disorders		Hiccups	
Gastrointestinal disorders	Constipation	Abdominal distension	Dry mouth
		Abdominal pain	Dysphagia
		Diarrhoea	Eructation
		Dyspepsia	Haemorrhoids
		Flatulence	Tongue coated
		Nausea	Vomiting
Skin and subcutaneous tissue disorders		Alopecia	Erythema
		Urticaria	Pruritus
			Rash
Musculoskeletal and connective tissue disorders			Back pain
			Pain in extremities
General disorders and administration site conditions	Fatigue	Asthenia	Feeling hot
			Non-cardiac chest pain
			Product taste abnormal
Investigations		Liver transaminases increased	Blood bilirubin increased
		Blood alkaline phosphatase increased	Blood creatine phosphokinase increased
		Blood creatinine increased	Blood creatine Phosphokinase MB increased

		Electrocardiogram QT prolonged	Blood urea increased
			Electrocardiogram ST segment depression
			Electrocardiogram ST-T segment abnormal
			Myoglobin blood increased
			Neutrophil count increased
			Troponin increased

Post-marketing data indicates that the adverse reactions profile is generally similar to that seen in clinical trials.

Description of selected adverse reactions

Netupitant:
No common adverse reactions are attributable to netupitant, the new component of the fixed combination.

Palonosetron:
Cases of constipation with faecal impaction requiring hospitalisation have been reported in association with palonosetron 0.75 mg.

In addition, eye swelling, dyspnoea and myalgia have been reported as adverse reactions with oral palonosetron but not observed during the development of netupitant and palonosetron hydrochloride combination. All these reactions were uncommon.

Very rare cases of anaphylaxis, anaphylactic/anaphylactoid reactions and shock have been reported from the post-marketing use of intravenous palonosetron. The signs may include hives, itch, angioedema, low blood pressure, throat tightness, chest tightness, dyspnoea, loss of consciousness.

Cases of serotonin syndrome have reported with palonosetron alone. The signs may include tremor, agitation, sweating, myoclonic movements, hypertonia and fever.

The safety profile of Akynzeo 235 mg/0.25 mg concentrate for solution for infusion was similar to that seen with Akynzeo 300 mg/0.5 mg hard capsules.

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

Based on the experience with healthy subjects exposed to oral netupitant 600 mg in combination with palonosetron 1.50 mg the potential acute symptoms of overdose are headache, dizziness, constipation, anxiety, palpitations, euphoric mood and pain in the legs. In case of overdose, the medicinal product should be discontinued and general supportive treatment and monitoring should be provided. Because of the antiemetic activity of netupitant and palonosetron, emesis induced by a medicinal product may not be effective. Dialysis studies have not been performed. However, due to the large volume of distribution of palonosetron and netupitant, dialysis is unlikely to be an effective treatment for overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiemetics and antinauseants, serotonin (5-HT_3) antagonists; ATC code: A04AA55

Mechanism of action

Netupitant is a selective antagonist of human substance P/neurokinin 1 (NK_1) receptors.

Fosnetupitant is the prodrug of netupitant and when administered intravenously is converted rapidly to netupitant (see section 5.2).

Palonosetron is a 5-HT_3 receptor antagonist with a strong binding affinity for this receptor and little or no affinity for other receptors. Chemotherapeutic substances produce nausea and vomiting by stimulating the release of serotonin from the enterochromaffin cells of the small intestine. Serotonin then activates 5-HT_3 receptors located on vagal afferents to initiate the vomiting reflex.

Delayed emesis has been associated with the activation of tachykinin family neurokinin 1 (NK_1) receptors (broadly distributed in the central and peripheral nervous systems) by substance P. As shown in *in vitro* and *in vivo* studies, netupitant inhibits substance P mediated responses.

Netupitant was shown to cross the blood brain barrier with a NK_1 receptor occupancy of 92.5%, 86.5%, 85.0%, 78.0%, and 76.0% in striatum at 6, 24, 48, 72, and 96 hours, respectively, after administration of 300 mg netupitant.

Clinical efficacy and safety

Oral administration of Akynzeo in combination with dexamethasone has been shown to prevent acute and delayed nausea and vomiting associated with highly and moderately emetogenic cancer chemotherapy in two separate pivotal studies.

Highly Emetogenic Chemotherapy (HEC) study
In a multicenter, randomized, parallel, double-blind, controlled clinical study of 694 patients, the efficacy and safety of single doses of oral netupitant in combination with oral palonosetron was compared with a single oral dose of palonosetron in cancer patients receiving a chemotherapy regimen that included cisplatin (median dose = 75 mg/m^2). The efficacy of Akynzeo was assessed in 135 patients who received a single oral dose (netupitant 300 mg and palonosetron 0.5 mg) and 136 patients who received oral palonosetron 0.5 mg alone.

Treatment regimens for the Akynzeo and the palonosetron 0.5 mg arms are displayed in Table 2 below.

Table 2: Oral antiemetic treatment regimen — HEC study

Treatment regimen	Day 1	Days 2 to 4
Akynzeo	Akynzeo (Netupitant 300 mg + Palonosetron 0.5 mg) Dexamethasone 12 mg	Dexamethasone 8 mg once a day
Palonosetron	Palonosetron 0.5 mg Dexamethasone 20 mg	Dexamethasone 8 mg twice a day

The primary efficacy endpoint was complete response (CR) rate (defined as no emetic episodes, no rescue medication) within 120 hours (overall phase) after the start of the highly emetogenic chemotherapy administration.
A summary of the key results from this study is shown in Table 3 below.

Table 3: Proportion of patients receiving cisplatin chemotherapy responding by treatment group and phase

	Akynzeo N=135 %	Palonosetron 0.5 mg N=136 %	p-value
Primary endpoint			
Complete response			
Overall phase[§]	89.6	76.5	0.004
Major secondary endpoints			
Complete response			
Acute phase[‡]	98.5	89.7	0.007
Delayed phase[†]	90.4	80.1	0.018
No emesis			
Acute phase	98.5	89.7	0.007
Delayed phase	91.9	80.1	0.006
Overall phase	91.1	76.5	0.001
No significant nausea			
Acute phase	98.5	93.4	0.050
Delayed phase	90.4	80.9	0.004
Overall phase	89.6	79.4	0.021

[‡]Acute phase: 0 to 24 hours post-cisplatin treatment.
[†]Delayed phase: 25 to 120 hours post-cisplatin treatment.
[§]Overall: 0 to 120 hours post-cisplatin treatment.

Moderately Emetogenic Chemotherapy (MEC) study
In a multicenter, randomized, parallel, double-blind, active-controlled, superiority study, the efficacy and safety of a single oral dose of Akynzeo was compared with a single oral dose of palonosetron 0.5 mg in cancer patients scheduled to receive the first cycle of an anthracycline and cyclophosphamide regimen for the treatment of a solid malignant tumour. At the time of the study, anthracycline-cyclophosphamide containing chemotherapy regimens were considered to be moderately emetogenic. Recent guidance has updated these regimens to highly emetogenic.
All patients received a single oral dose of dexamethasone.

Table 4: Oral antiemetic treatment regimen – MEC study

Treatment regimen	**Day 1**	**Days 2 to 3**
Akynzeo	Akynzeo (Netupitant 300 mg + Palonosetron 0.5 mg) Dexamethasone 12 mg	No antiemetic treatment
Palonosetron	Palonosetron 0.5 mg Dexamethasone 20 mg	No antiemetic treatment

After completion of cycle 1, patients had the option to participate in a multiple-cycle extension, receiving the same treatment as assigned in cycle 1. There was no pre-specified limit of the number of repeat consecutive cycles for any patient. A total of 1450 patients (Akynzeo n=725; Palonosetron n=725) received study medication. Of these, 1438 patients (98.8%) completed cycle 1 and 1286 patients (88.4%) continued treatment in the multiple-cycle extension. A total of 907 patients (62.3%) completed the multiple-cycle extension up to a maximum of eight treatment cycles.

A total of 724 patients (99.9%) were treated with cyclophosphamide. All patients were additionally treated with either doxorubicin (68.0%) or epirubicin (32.0%).

The primary efficacy endpoint was the CR rate in the delayed phase, 25-120 hours after the start of the chemotherapy administration.

A summary of the key results from this study is shown in the table 5 below.

Table 5: Proportion of patients receiving anthracycline and cyclophosphamide chemotherapy responding by treatment group and phase – cycle 1

	Akynzeo N=724 %	Palonosetron 0.5 mg N=725 %	p-value*
Primary endpoint			
Complete response			
Delayed phase[†]	76.9	69.5	0.001
Major secondary endpoints			
Complete response			
Acute phase[‡]	88.4	85.0	0.047
Overall phase[§]	74.3	66.6	0.001
No emesis			
Acute phase	90.9	87.3	0.025
Delayed phase	81.8	75.6	0.004
Overall phase	79.8	72.1	<0.001
No significant nausea			
Acute phase	87.3	87.9	N.S.
Delayed phase	76.9	71.3	0.014
Overall phase	74.6	69.1	0.020

* p-value from Cochran-Mantel-Haenszel test, stratified by age class and region.
[‡]Acute phase: 0 to 24 hours after anthracycline and cyclophosphamide regimen
[†]Delayed phase: 25 to 120 hours after anthracycline and cyclophosphamide regimen
[§]Overall: 0 to 120 hours after anthracycline and cyclophosphamide regimen

Patients continued into the Multiple-Cycle extension for up to 7 additional cycles of chemotherapy. Antiemetic activity of Akynzeo was maintained throughout repeat cycles for those patients continuing in each of the multiple cycles.
The impact of nausea and vomiting on patients' daily lives was assessed using the Functional Living Index–Emesis (FLIE). The proportion of patients with Overall no impact on daily life was 6.3% higher (p value =0.005) in the Akynzeo group (78.5%) than in the palonosetron group (72.1%).

Multiple-cycle safety study in patients receiving either Highly Emetogenic Chemotherapy or Moderately Emetogenic Chemotherapy
In a separate study, a total of 413 patients undergoing initial and repeat cycles of chemotherapy (including carboplatin, cisplatin, oxaliplatin, and doxorubicin regimens), were randomized to receive either Akynzeo (n=309) or aprepitant and palonosetron (n=104). Safety and efficacy were maintained throughout all cycles.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Akynzeo in one or more subsets of the paediatric population in prevention of chemotherapy-induced nausea and vomiting, as per PIP decision in the granted indication. See section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

Absorption

Netupitant
Absolute netupitant bioavailability data are not available in humans; based on data from two studies with intravenous netupitant, the bioavailability in humans is estimated to be greater than 60%.
In single dose oral studies, netupitant was measurable in plasma between 15 minutes and 3 hours after dosing. Plasma concentrations followed a first order absorption process and reached C_{max} in approximately 5 hours. There was a supra-proportional increase in C_{max} and AUC parameters for doses from 10 mg to 300 mg.
In 82 healthy subjects given a single oral dose of netupitant 300 mg, maximum plasma netupitant concentration (C_{max}) was 486 ±268 ng/mL (mean ± SD) and median time to maximum concentration (T_{max}) was 5.25 hours, the AUC was 15032 ± 6858 h.ng/mL. In a pooled analysis, females had a higher netupitant exposure compared to males; there was a 1.31-fold increase in C_{max}, a 1.02 fold increase for AUC and a 1.36 fold increase in half-life.
Netupitant $AUC_{0-\infty}$ and C_{max} increased by 1.1 fold and 1.2 fold, respectively, after a high fat meal.

Fosnetupitant
After single dose administration of Akynzeo, administered as a 30-minute infusion to healthy subjects and cancer patients, fosnetupitant achieved C_{max} at the end of the infusion with an apparent terminal half-life less than 1 hour. Within 30 minutes of completion of the infusion, the concentration of fosnetupitant decreased to less than 1% of the C_{max}. The pharmacokinetic parameters of netupitant and palonosetron were similar to those observed after Akynzeo 300 mg/0.5 mg hard capsules.

Table 6: PK Parameters (mean and CV%) After Single Dose Administration Akynzeo Concentrate for Solution for Infusion in Healthy Volunteers (HVs) and Cancer Patients

		Fosnetupitant	Netupitant	Palonosetron[2]
C_{max} (ng/mL)	HVs	6431 (14)	841 (21)	2.1 (61)
	Patients	3478 (45)	590 (28)	0.8 (35)
t_{max}[1] (h)	HVs	0.5 (0.25 – 0.5)	0.5 (0.5 – 0.4)	0.55
	Patients	0.5 (0.5 – 0.6)	0.6 (0.5 – 4)	0.6 (0.5 – 6)
AUC (ng*h/mL)	HVs	2938 (12)	13854 (21)	35 (33)
	Patients	1401 (46)	15588 (32)	36 (30)
$t_{1/2}$ (h)	HVs	0.96 (57)	36.1 (19)	43 (32)
	Patients	0.75 (54)	144 (50)	58 (47)

[1] median (min-max); [2] IV bolus in HVs

Fosnetupitant C_{max} and AUC were lower in patients than in healthy subjects, although the systemic exposures to netupitant were comparable.

In healthy subjects, there was a dose-proportional increase in the systemic exposure of fosnetupitant with the dose increase of fosnetupitant from 17.6 to 353 mg

Palonosetron
Following oral administration, palonosetron is well absorbed with its absolute bioavailability reaching 97%. After single oral doses using buffered solution mean maximum palonosetron concentrations (C_{max}) and area under the concentration-time curve ($AUC_{0-\infty}$) were dose proportional over the dose range of 3.0 to 80 mcg/kg in healthy subjects.
In 36 healthy male and female subjects given a single oral dose of 0.5 mg palonosetron, maximum plasma concentration (C_{max}) was 0.81 ± 1.66 ng/mL (mean ± SD) and time to maximum concentration (T_{max}) was 5.1 ± 1.7 hours. In female subjects (n=18), the mean AUC was 35% higher and the mean

C_{max} was 26% higher than in male subjects (n=18). In 12 cancer patients given a single oral dose of palonosetron 0.5 mg one hour prior to chemotherapy, C_{max} was 0.93 ± 0.34 ng/mL and T_{max} was 5.1 ± 5.9 hours. The AUC was 30% higher in cancer patients than in healthy subjects. A high fat meal did not affect the C_{max} and AUC of oral palonosetron.

Distribution

Netupitant
After a single oral 300 mg dose administration in cancer patients, netupitant disposition was characterised by a two compartment model with an estimated median systemic clearance of 20.5 L/h and a large distribution volume in the central compartment (486 L). Human plasma protein binding of netupitant and its two major metabolites M1 and M3 is > 99% at concentrations ranging from 10 to 1500 ng/mL. The third major metabolite, M2, is > 97% bound to plasma proteins.

Fosnetupitant
The mean ± SD volume of distribution (Vz) of fosnetupitant in healthy subjects and in patients was 124 ± 76 L and 296 ±535 L, respectively. The human plasma protein binding of fosnetupitant was 92% at 1 micromolar and 95% at 10 micromolar. The free fraction was in the range 5 to 8%.

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

Biotransformation

Netupitant
Three metabolites have been detected in human plasma at netupitant oral doses of 30 mg and higher (the desmethyl derivative, M1; the N-oxide derivative, M2; the OH-methyl derivative, M3). *In vitro* metabolism studies have suggested that CYP3A4 and, to a lesser extent, CYP2D6 and CYP2C9 are involved in the metabolism of netupitant. After administration of a single oral dose of 300 mg netupitant, mean plasma netupitant/plasma radioactivity ratios ranged from 0.13 to 0.49 over 96 h post-dose. The ratios were time dependent with values decreasing gradually beyond 24 h post-dose, indicating that netupitant is being rapidly metabolised. Mean C_{max} was approximately 11%, 47% and 16% of the parent for M1, M2 and M3 respectively; M2 had the lowest AUC relative to the parent (14%) whereas M1 and M3 AUC were approximately 29% and 33% of the parent, respectively. M1, M2 and M3 metabolites were all shown to be pharmacologically active in an animal pharmacodynamic model, where M3 was most potent and M2 least active.

Fosnetupitant
Fosnetupitant is rapidly converted *in vivo* to netupitant by metabolic hydrolysis. In patients receiving Akynzeo 235 mg/0.25 mg concentrate for solution for infusion intravenously, netupitant exposure was 17-fold fosnetupitant exposure, as determined by their AUC ratio. Netupitant metabolites M1, M2 and M3 were rapidly generated from the released netupitant. In patients, metabolite M1, M2 and M3 exposures were 32%, 21% and 28% of netupitant exposure, as determined by their AUC ratio. The median t_{max} for M1, M2, and M3 were 12, 2 and 12 hours, respectively.

Palonosetron
Palonosetron is eliminated by multiple routes with approximately 50% metabolised to form two primary metabolites: N-oxide-palonosetron and 6-S-hydroxy-palonosetron. These metabolites each have less than 1% of the 5-HT_3 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

Netupitant
Following administration of a single dose of Akynzeo, netupitant is eliminated from the body in a multi-exponential fashion, with an apparent mean elimination half-life of 88 hours in cancer patients. Renal clearance is not a significant elimination route for netupitant-related entities. The mean fraction of an oral dose of netupitant excreted unchanged in urine is less than 1%; a total of 3.95% and 70.7% of the radioactive dose was recovered in the urine and faeces, respectively.
Approximately half the radioactivity administered orally as [14C]-netupitant was recovered from urine and faeces within 120 h of dosing. Elimination via both routes was estimated to be complete by Day 29-30 post-dose.

Fosnetupitant
After intravenous Akynzeo 235 mg/0.25 mg concentrate for solution for infusion administration, fosnetupitant plasma concentrations declined according to a biexponential profile. Thirty minutes after the end of the infusion, the mean plasma concentration of fosnetupitant was less than 1% of $C_{max.}$

Palonosetron
Following administration of a single oral 0.75 mg dose of [14C]-palonosetron to six healthy subjects, 85% to 93% of the total radioactivity was excreted in urine, and 5% to 8% was eliminated in faeces. The amount of unchanged palonosetron excreted in the urine represented approximately 40% of the administered dose. In healthy subjects given palonosetron capsules 0.5 mg, the terminal elimination half-life (t½) of palonosetron was 37 ± 12 hours (mean ± SD), and in cancer patients, t½ was 48 ± 19 hours. After a single dose of approximately 0.75 mg intravenous palonosetron, the total body clearance of palonosetron in healthy subjects was 160 ± 35 mL/h/kg (mean ± SD) and renal clearance was 66.5± 18.2 mL/h/kg.

Special populations

Hepatic impairment

Netupitant
Maximum concentrations and total exposure of netupitant were increased in subjects with mild (n=8), moderate (n=8), and severe (n=2) hepatic impairment compared to matching healthy subjects, although there was pronounced individual variability in both hepatically-impaired and healthy subjects. Exposure to netupitant (C_{max}, AUC_{0-t} and $AUC_{0-\infty}$) compared to matching healthy subjects was 11%, 28% and 19% higher in mild and 70%, 88% and 143% higher in moderate hepatically-impaired subjects, respectively. As such, no dose adjustment is necessary for patients with mild to moderate hepatic impairment. Limited data exist in patients with severe hepatic impairment (Child Pugh score ≥9).

Palonosetron
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.

Renal impairment

Netupitant
No specific studies were performed to evaluate netupitant in patients with renal impairment. In the ADME trial, less than 5% of all netupitant-related material was excreted in urine and less than 1% of the netupitant dose was eliminated unchanged in the urine and therefore any accumulation of netupitant or metabolites after a single dose would be negligible. Furthermore, the population PK study showed no correlation between PK parameters of netupitant and markers of renal dysfunction.

Palonosetron
Mild to moderate renal impairment does not significantly affect palonosetron PK parameters. Total systemic exposure to intravenous palonosetron increased by approximately 28% in patients with severe impairment relative to healthy subjects. In a population PK study, patients with a reduced

creatinine clearance (CL_{CR}) also had a reduced palonosetron clearance, but this reduction would not result in a significant change in palonosetron exposure.

Therefore, Akynzeo can be administered without dose adjustment in patients with renal impairment.

Neither netupitant nor palonosetron have been evaluated in patients with end-stage renal disease.

5.3 Preclinical safety data

Palonosetron

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. Degeneration of seminiferous epithelium was associated with palonosetron following a one-month oral repeat dose toxicity study in rats. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. Only limited data from animal studies are available regarding the placental transfer (see section 4.6). Palonosetron is not mutagenic. High doses of palonosetron (each dose causing at least 15 times the human therapeutic exposure) applied daily for two years caused an increased rate of liver tumours, endocrine neoplasms (in thyroid, pituitary, pancreas, adrenal medulla) and skin tumours in rats but not in mice. The underlying mechanisms are not fully understood, but because of the high doses employed and since the medicinal product is intended for single application in humans, these findings are not considered relevant for clinical use.

Netupitant and combination with palonosetron

Effects in non-clinical studies based on safety pharmacology and single and repeated dose toxicity were observed only at exposures considered in excess of the maximum human exposure, indicating little relevance to clinical use. Phospholipidosis (foamy macrophages) has been observed with the administration of netupitant after repeated administration in rats and dogs. The effects were reversible or partially reversible after the recovery period. The significance of these findings in humans is unknown.

Non-clinical studies indicate that netupitant and its metabolites and the combination with palonosetron only at very high concentrations may block ion channels involved in ventricular de- and re-polarisation and prolong action potential duration. Reproductive studies in animals with netupitant do not indicate direct or indirect harmful effects with respect to fertility, parturition or postnatal development. An increased incidence of positional foetal abnormalities of the limbs and paws, fused sternebrae and agenesis of accessory lung lobe were observed following daily administration of netupitant in rabbits at 10 mg/kg/day and higher during the period of organogenesis. In a pilot dose range finding study in rabbits, cleft palate, microphtalmia and aphakia were observed in four foetuses from one litter in the 30 mg/kg/day group. The relevance of these findings in humans is unknown. No data from animal studies with netupitant are available regarding placental transfer and lactation. Netupitant is not mutagenic.

Fosnetupitant

Daily intravenous administration of fosnetupitant in rats (at 3 times the human AUC for netupitant at the recommended single dose to be given with each cycle of chemotherapy) during the period of organogenesis produced delayed ossification of pubis. No effects on embryo-fetal development were observed with daily administration of up to 13 mg/kg fosnetupitant in rats (2 times the human AUC for netupitant at the recommended single dose to be given with each cycle of chemotherapy). Due to the limited systemic exposure to fosnetupitant in pregnant rats, it is not possible to provide an AUC-based comparison of fosnetupitant exposure in rats and humans. An increase in resorptions was observed with daily intravenous administration of fosnetupitant at 6 mg/kg/day and higher in rabbits (9 times the human AUC for fosnetupitant and 0.4 times the human AUC for netupitant at the

recommended single dose to be given with each cycle of chemotherapy) during the period of organogenesis. No effects were observed in rabbits at 3 mg/kg/day (5.4 times the human AUC for fosnetupitant and 0.4 times the human AUC for netupitant at the recommended single dose to be given with each cycle of chemotherapy). Daily intravenous administration of 39 mg/kg fosnetupitant in rats (3 times the AUC for netupitant at the recommended single dose to be given with each cycle of chemotherapy) during organogenesis through lactation produced lower bodyweight in offspring at birth through maturation, and delayed physical development (pinna detachment, eye opening, and preputial separation). These effects were associated with maternal toxicity (reduced weight gain and food consumption). No effects occurred in offspring or dams at 13 mg/kg/day (2 times the human AUC for netupitant at the recommended single dose to be given with each cycle of chemotherapy).

Fosnetupitant–palonosetron combination

Intravenous and Intra-arterial administration in rabbits: for the clinical signs very slight to mild erythema were observed. No changes were noted at microscopic examination.
Paravenous administration (a non-intended clinical route/misapplication) in rabbits: for the clinical signs very slight to mild erythema and very slight oedema were observed. At microscopic examination chronic inflammation (from mild to moderate), epidermal hyperplasia (from minimal to mild) of dermis were reported.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Disodium edetate (E386)
Sodium hydroxide (E524) (for pH adjustment)
Hydrochloric acid (E507) (1M for pH adjustment)
Water

6.2 Incompatibilities

Akynzeo concentrate for solution for infusion is incompatible with any solutions containing divalent cations (e.g., Ca^{2+}, Mg^{2+}), including Hartman's and lactated Ringer's solutions.

Akynzeo concentrate for solution for infusion should not be infused simultaneously or mixed with other intravenous substances, additives or medicinal products unless compatibility has been demonstrated. If the same intravenous line is used for sequential infusion of several different medicinal products, the line should be flushed before and after infusion of Akynzeo with sodium chloride 9 mg/ml (0.9%) solution for injection.

6.3 Shelf life

3 years.

Store the diluted solution below 25°C.

Chemical, physical and microbiological in-use stability after dilution has been demonstrated for 24 hours at 25°C.

6.4 Special precautions for storage

Store below 25°C.
Keep the vial in the outer carton in order to protect from light.
For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Single-dose 20 mL glass vials with 20 mm rubber stoppers and 20 mm aluminium cap seals.
Pack of 1 vial.

6.6 Special precautions for disposal and other handling

Akynzeo must be diluted prior to administration.

Preparation of Akynzeo

Step 1	Aseptically prepare an infusion vial or bag filled with 30 mL of 5% glucose injection, or sodium chloride 9 mg/ml (0.9%) solution for injection.
Step 2	Aseptically withdraw the entire volume of concentrate from the AKYNZEO vial and transfer it into the infusion vial or bag containing 30 mL of 5% glucose injection or sodium chloride 9 mg/ml (0.9%) solution for injection to yield a total volume of 50 mL.
Step 3	Before administration, inspect the final diluted solution for particulate matter and discolouration. Discard the vial or bag if particulates and/or discolouration are observed.

Akynzeo must not be diluted or mixed with solutions for which physical and chemical compatibility has not been established (see section 6.2).

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

7. MARKETING AUTHORISATION HOLDER

Helsinn Birex Pharmaceuticals Ltd.
Damastown
Mulhuddart
Dublin 15
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1001/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27 May 2015
Date of latest renewal: 9 January 2020

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Akynzeo 300 mg/0.5 mg oral suspension in sachet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet contains 300 mg of netupitant and palonosetron hydrochloride equivalent to 0.5 mg of palonosetron.

Excipients with known effect

Each sachet contains:

137.5 mg of sodium citrate dihydrate (32.2 mg of sodium)
10 mg of potassium sorbate (2.6 mg of potassium)
8 863.3 mg of sorbitol liquid (non-crystallising) (E420) (6 204.3 mg of sorbitol)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral suspension.

White to off white homogeneous suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Akynzeo is indicated in adults for the:
- Prevention of acute and delayed nausea and vomiting associated with highly emetogenic cisplatin-based cancer chemotherapy.
- Prevention of acute and delayed nausea and vomiting associated with moderately emetogenic cancer chemotherapy.

4.2 Posology and method of administration

Posology

One 300 mg/0.5 mg sachet should be administered approximately one hour prior to the start of each chemotherapy cycle.

The recommended oral dexamethasone dose should be reduced by approximately 50 % when co-administered with netupitant/palonosetron sachets (see section 4.5 and clinical studies administration schedule in section 5.1).

Special populations

Elderly people
No dose adjustment is necessary for elderly patients. Caution should be exercised when using this medicinal product in patients over 75 years, due to the long half-life of the active substances and the limited experience in this population.

Renal impairment
Dose adjustment is not considered necessary in patients with mild to severe renal impairment. Renal excretion for netupitant is negligible. Mild to moderate renal impairment does not significantly affect palonosetron pharmacokinetic parameters. Total systemic exposure to intravenous palonosetron increased by approximately 28% in severe renal impairment relative to healthy subjects. The pharmacokinetics of palonosetron or netupitant has not been studied in subjects with end-stage renal disease requiring hemodialysis and no data on the effectiveness or safety of netupitant/palonosetron sachets in these patients are available. Therefore, use in these patients should be avoided.

Hepatic impairment
No dose adjustment is necessary for patients with mild or moderate hepatic impairment (Child-Pugh score 5-8). Limited data exist in patients with severe hepatic impairment (Child Pugh score ≥ 9). As use in patients with severe hepatic impairment may be associated with increased exposure of netupitant, this medicinal product should be used with caution in these patients (see sections 4.4 and 5.2).

Paediatric population

The safety and efficacy of Akynzeo sachets in the paediatric population have not been established. No data are available.

Method of administration

For oral use.

It can be taken with or without food.

Squeeze the entire contents of the sachet directly into the mouth.

4.3 Contraindications

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

Pregnancy (see section 4.6).

4.4 Special warnings and precautions for use

Constipation

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 (see section 4.8).

Serotonin syndrome

There have been reports of serotonin syndrome with the use of 5-HT_3 antagonists either alone or in combination with other serotonergic medicinal products (including selective serotonin reuptake inhibitors (SSRIs) and serotonin noradrenaline reuptake inhibitors (SNRIs). Appropriate observation of patients for serotonin syndrome-like symptoms is advised (see section 4.8).

QT prolongation

An ECG study was conducted in adult male and female healthy volunteers with oral netupitant either 200 or 600 mg administered in combination with oral palonosetron 0.5 or 1.5 mg, respectively. The study demonstrated no clinically important effects on ECG parameters: the largest point estimate of the placebo and baseline corrected QTc interval was 7.0 ms (one-sided upper 95% confidence

limit 8.8 ms), observed 16 hours after the administration of supratherapeutic doses (600 mg netupitant and 1.5 mg palonosetron). Upper 95% confidence limit of the point estimates of placebo and baseline corrected QTcI was constantly within 10 ms at all time points over 2 days after study substance administration.

However, since netupitant/palonosetron sachets contain a 5-HT_3 receptor antagonist, caution should be exercised in concomitant use with medicinal products that increase the QT interval or 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, bradyarrhythmia, conduction disturbances and in patients taking anti-arrhythmic medicinal products or other medicinal products that lead to QT prolongation or electrolyte abnormalities. Hypokalaemia and hypomagnesaemia should be corrected prior to administration.

Caution should be exercised in patients with severe hepatic impairment since limited data are available in these patients.

This medicinal product should be used with caution in patients receiving concomitant orally administered active substances that are metabolised primarily through CYP3A4 and with a narrow therapeutic range (see section 4.5).

Chemotherapeutic agents that are substrates for CYP3A4

Netupitant is a moderate inhibitor of CYP3A4 and can increase the exposure of chemotherapeutic agents that are substrates for CYP3A4 e.g. docetaxel (see section 4.5). Therefore, patients should be monitored for increased toxicity of chemotherapeutic agents that are substrates for CYP3A4, including irinotecan. Furthermore, netupitant may also affect the efficacy of chemotherapeutic agents that need activation by CYP3A4 metabolism.

Excipients

Sorbitol
Patients with hereditary fructose intolerance (HFI) should not take/be given this medicinal product.

Sodium
This medicinal product contains 32.2 mg sodium per sachet, equivalent to 1.61% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Potassium
This medicinal product contains 2.60 mg potassium per sachet. To be taken into consideration by patients with reduced kidney function or patients on a controlled potassium diet.

4.5 Interaction with other medicinal products and other forms of interaction

When netupitant/palonosetron sachets are used concomitantly with another CYP3A4 inhibitor, netupitant plasma concentrations could be elevated. When this medicinal product is used concomitantly with medicinal products that induce CYP3A4 activity, netupitant plasma concentrations could be reduced and this may result in decreased efficacy. This medicinal product can increase plasma concentrations of concomitantly administered medicinal products that are metabolised via CYP3A4.

In humans, netupitant is eliminated mainly by hepatic metabolism mediated by CYP3A4 with a marginal renal excretion. At a dose of 300 mg in humans, netupitant is a substrate and moderate inhibitor of CYP3A4. Palonosetron is eliminated from the body through both renal excretion and metabolic pathways, with the latter mediated via multiple CYP enzymes. 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.

Interaction between oral netupitant and oral palonosetron

No clinically relevant pharmacokinetic interactions have been observed between oral netupitant and oral palonosetron.

Interaction with CYP3A4 substrates

Dexamethasone
Co-administration of a single dose of 300 mg netupitant with a dexamethasone regimen (20 mg on Day 1, followed by 8 mg twice daily from Day 2 to Day 4) significantly increased the exposure to dexamethasone in a time and dose dependent manner. The AUC_{0-24} (Day 1), the AUC_{24-36} (Day 2) and the AUC_{84-108} and $AUC_{84-\infty}$ (Day 4) of dexamethasone increased 2.4-fold, with co-administration of 300 mg netupitant. The pharmacokinetic profile of netupitant was unchanged when administered in combination with dexamethasone.
As such, the oral dexamethasone dose should be reduced by approximately 50% when co-administered with netupitant/palonosetron sachets (see section 4.2).

Chemotherapeutic medicinal products (docetaxel, etoposide, cyclophosphamide)
Exposure to docetaxel and etoposide was increased 37% and 21%, respectively, when co-administered with netupitant/palonosetron sachets. No consistent effect was seen with cyclophosphamide after netupitant co-administration.

Oral contraceptives
Netupitant/palonosetron sachets, when given with a single oral dose of 60 mcg ethinylestradiol and 300 mcg levonorgestrel had no significant effect on the AUC of ethinylestradiol and increased the AUC of levonorgestrel by 1.4-fold; clinical effects on the efficacy of hormonal contraception are unlikely. No relevant changes of netupitant and palonosetron pharmacokinetics were observed.

Erythromycin and midazolam
Exposure to erythromycin and midazolam was increased approximately 1.3 and 2.4 fold, respectively, when each was co-administered with netupitant. These effects were not considered clinically important. The pharmacokinetic profile of netupitant was unaffected by the concomitant administration of either midazolam or erythromycin. The potential effects of increased plasma concentrations of midazolam or other benzodiazepines metabolised via CYP3A4 (alprazolam, triazolam) should be considered when coadministering these active substances with netupitant/palonosetron sachets.

Serotonergic medicinal products (e.g. SSRIs and SNRIs)

There have been reports of serotonin syndrome following concomitant use of 5-HT_3 antagonists and other serotonergic medicinal products (including SSRIs such as fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram or escitalopram and SNRIs such as venlafaxine or duloxetine) (see section 4.4).

Effect of other medicinal products on the pharmacokinetics of Akynzeo

Netupitant is mainly metabolised by CYP3A4; therefore, co-administration with medicinal products that inhibit or induce CYP3A4 activity may influence plasma concentrations of netupitant. Consequently, concomitant administration with strong CYP3A4 inhibitors (e.g., ketoconazole) should be approached with caution and concomitant administration with strong CYP3A4 inducers (e.g., rifampicin) should be avoided. Moreover, this medicinal product should be used with caution in patients receiving concomitant orally administered active substances with a narrow therapeutic range that are primarily metabolised by CYP3A4, such as cyclosporine, tacrolimus, sirolimus, everolimus, alfentanil, diergotamine, ergotamine, fentanyl, and quinidine.

Effect of ketoconazole and rifampicin

Administration of the CYP3A4 inhibitor ketoconazole with netupitant/palonosetron sachets increased the AUC of netupitant 1.8 fold and C_{max} 1.3 fold when compared to the administration of netupitant/palonosetron sachets alone. Co-administration with ketoconazole did not affect the pharmacokinetics of palonosetron.

Administration of the CYP3A4 inducer rifampicin with Akynzeo alone decreased the AUC of netupitant 5.2 fold and C_{max} 2.6 fold. Co-administration of rifampicin did not affect the pharmacokinetics of palonosetron. Consequently, concomitant administration with strong CYP3A4 inhibitors (e.g., ketoconazole) should be approached with caution and concomitant administration with strong CYP3A4 inducers (e.g. rifampicin) should be avoided.

Additional interactions

Netupitant/palonosetron sachets are unlikely to interact with medicinal products which are P-gp substrates. Netupitant is not a substrate for P-gp. When netupitant was administered on Day 8 of a 12-day regimen of digoxin, no changes in digoxin pharmacokinetics were observed.

Inhibition of the efflux transported BCRP and glucuronidation isozyme UGT2B7 by netupitant and its metabolites is unlikely and, if it occurs, of scarce clinical relevance.

In vitro data shows that netupitant inhibits UGT2B7, the magnitude of such an effect in the clinical setting is not established. Caution is recommended when netupitant is combined with an oral substrate of this enzyme (e.g.zidovudine, valproic acid, morphine).

In vitro data suggests that netupitant inhibits the efflux of transporter BCRP. The clinical relevance of this effect is not established.

In vitro data show that netupitant is a P-gp inhibitor. In a study performed in healthy volunteers, netupitant does not affect the exposure of digoxin, a P-gp substrate, whereas it increases its C_{max} by 1.09 fold [90%CI 0.9-1.31]. It is not excluded that this effect may be more marked, and then clinically relevant, in cancer patients, notably those having abnormal renal function. Therefore, caution is recommended when netupitant is combined with digoxin or with other P-gp substrates such as dabigatran, or colchicine.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/ contraception in females

Women of childbearing potential should not be pregnant or become pregnant while on treatment with netupitant/palonosetron sachets. A pregnancy test should be performed on all pre-menopausal women prior to treatment. Women of childbearing potential must use effective contraception during therapy and up to one month after treatment with this medicinal product.

Pregnancy

Netupitant
There are no data about the use of netupitant in pregnant women. Studies in animals have shown reproductive toxicity including teratogenic effects in rabbit without safety margin (see section 5.3).

Palonosetron
There are no data about the use of palonosetron in pregnant women. Animal data do not indicate direct or indirect harmful effects of palonosetron with the respect to reproductive toxicity (see section 5.3).

Netupitant/palonosetron sachets are contraindicated during pregnancy (see section 4.3).

Breast-feeding

It is unknown whether palonosetron or netupitant are excreted in human milk. A risk to the suckling child cannot be excluded. Netupitant/palonosetron sachets should not be used during breast-feeding. Breast-feeding should be discontinued during treatment with this medicinal product and for 1 month after the last dose.

Fertility

Netupitant
No effect on fertility has been observed in animal studies.

Palonosetron
Degeneration of seminiferous epithelium has been observed in rat study (see section 5.3).

4.7 Effects on ability to drive and use machines

Netupitant/palonosetron sachets have moderate influence on the ability to drive and use machines. Since it may induce dizziness, somnolence or fatigue, patients should be cautioned not to drive or use machines if such symptoms occur.

4.8 Undesirable effects

Summary of the safety profile

Common adverse reactions reported with netupitant/palonosetron sachets were headache (3.6%), constipation (3.0%) and fatigue (1.2%).

Tabulated list of adverse reactions

Adverse reactions are listed below by MedDRA body system organ class and frequency.

The following convention has been used for classification of frequency:
Very common (≥1/10),
Common (≥1/100 to <1/10),
Uncommon (≥1/1 000 to <1/100),
Rare (≥1/10 000 to <1/1 000),
Very rare (<1/10 000),
Not known (cannot be estimated from the available data).

Table1: Adverse reactions

System organ class	Common	Uncommon	Rare
Infections and infestations			Cystitis
Blood and lymphatic system disorders		Neutropenia	Leukopenia
		Leucocytosis	Lymphocytosis
Metabolism and nutrition disorders		Decreased appetite	Hypokalaemia
Psychiatric disorders		Insomnia	Acute psychosis
			Mood altered
			Sleep disorder
Nervous system disorders	Headache	Dizziness	Hypoaesthesia
			Somnolence
Eye disorders			Conjunctivitis
			Vision blurred
Ear and labyrinth disorders		Vertigo	Tinnitus
Cardiac disorders		Atrioventricular block first degree	Arrhythmia
		Cardiomyopathy	Atrioventricular block second degree
		Conduction disorder	Bundle branch block left
		Tachycardia	Bundle branch block right
			Mitral valve incompetence
			Myocardial ischaemia
			Ventricular extrasystoles
Vascular disorders		Hypertension	Flushing
			Hypotension
Respiratory, thoracic and mediastinal disorders		Hiccups	
Gastrointestinal disorders	Constipation	Abdominal distension	Dry mouth
		Abdominal pain	Dysphagia
		Diarrhoea	Eructation
		Dyspepsia	Haemorrhoids
		Flatulence	Tongue coated
		Nausea	Vomiting
Skin and subcutaneous tissue disorders		Alopecia	Erythema
		Urticaria	Pruritus
			Rash
Musculoskeletal and connective tissue disorders			Back pain
			Pain in extremities
General disorders and administration site conditions	Fatigue	Asthenia	Feeling hot
			Non-cardiac chest pain
			Product taste abnormal
Investigations		Liver transaminases increased	Blood bilirubin increased
		Blood alkaline phosphatase increased	Blood creatine phosphokinase increased
		Blood creatinine	Blood creatine phosphokinase

		increased	MB increased
		Electrocardiogram QT prolonged	Blood urea increased
			Electrocardiogram ST segment depression
			Electrocardiogram ST-T segment abnormal
			Myoglobin blood increased
			Neutrophil count increased
			Troponin increased

Post-marketing data indicates that the adverse reactions profile is generally similar to that seen in clinical trials.

Description of selected adverse reactions

Netupitant
No common adverse reactions are attributable to netupitant, the new component of the fixed combination.

Palonosetron
Cases of constipation with faecal impaction requiring hospitalisation have been reported in association with palonosetron 0.75 mg.

In addition, eye swelling, dyspnoea and myalgia as adverse reactions have been reported with oral palonosetron but not observed during the development of this medicinal product. All these reactions were uncommon.

Very rare cases of anaphylaxis, anaphylactic/anaphylactoid reactions and shock have been reported from the post-marketing use of intravenous palonosetron. The signs may include hives, itch, angioedema, low blood pressure, throat tightness, chest tightness, dyspnoea, loss of consciousness.

There have also been reports of serotonin syndrome. The signs may include tremor, agitation, sweating, myoclonic movements, hypertonia and fever.

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

Based on the experience with healthy subjects exposed to oral netupitant 600 mg in combination with palonosetron 1.50 mg the potential acute symptoms of overdose are headache, dizziness, constipation, anxiety, palpitations, euphoric mood and pain in the legs. In case of overdose, the medicinal product should be discontinued and general supportive treatment and monitoring should be provided. Because of the antiemetic activity of netupitant and palonosetron, emesis induced by a medicinal product may not be effective. Dialysis studies have not been performed. However, due to the large volume of distribution of palonosetron and netupitant, dialysis is unlikely to be an effective treatment for overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiemetics and antinauseants, serotonin (5-HT_3) antagonists; ATC code: A04AA55

Mechanism of action

Netupitant is a selective antagonist of human substance P/neurokinin 1 (NK_1) receptors. Palonosetron is a 5-HT_3 receptor antagonist with a strong binding affinity for this receptor and little or no affinity for other receptors. Chemotherapeutic substances produce nausea and vomiting by stimulating the release of serotonin from the enterochromaffin cells of the small intestine. Serotonin then activates 5-HT_3 receptors located on vagal afferents to initiate the vomiting reflex.

Delayed emesis has been associated with the activation of tachykinin family neurokinin 1 (NK_1) receptors (broadly distributed in the central and peripheral nervous systems) by substance P. As shown in *in vitro* and *in vivo* studies, netupitant inhibits substance P mediated responses.

Netupitant was shown to cross the blood brain barrier with a NK_1 receptor occupancy of 92.5%, 86.5%, 85.0%, 78.0%, and 76.0% in striatum at 6, 24, 48, 72, and 96 hours, respectively, after administration of 300 mg netupitant.

Clinical efficacy and safety

Oral administration of Akynzeo in combination with dexamethasone has been shown to prevent acute and delayed nausea and vomiting associated with highly and moderately emetogenic cancer chemotherapy in two separate pivotal studies.

Highly emetogenic chemotherapy (HEC) study
In a multicenter, randomized, parallel, double-blind, controlled clinical study of 694 patients, the efficacy and safety of single doses of oral netupitant in combination with oral palonosetron was compared with a single oral dose of palonosetron in cancer patients receiving a chemotherapy regimen that included cisplatin (median dose = 75 mg/m^2). The efficacy of Akynzeo was assessed in 135 patients who received a single oral dose (netupitant 300 mg and palonosetron 0.5 mg) and 136 patients who received oral palonosetron 0.5 mg alone.

Treatment regimens for the Akynzeo and the palonosetron 0.5 mg arms are displayed in the table below.

Table 2: Oral antiemetic treatment regimen — HEC study

Treatment regimen	Day 1	Days 2 to 4
Akynzeo	Akynzeo (Netupitant 300 mg + Palonosetron 0.5 mg) Dexamethasone 12 mg	Dexamethasone 8 mg once a day
Palonosetron	Palonosetron 0.5 mg Dexamethasone 20 mg	Dexamethasone 8 mg twice a day

The primary efficacy endpoint was complete response (CR) rate (defined as no emetic episodes, no rescue medication) within 120 hours (overall phase) after the start of the highly emetogenic chemotherapy administration.
A summary of the key results from this study is shown in Table 3 below.

Table 3: Proportion of patients receiving cisplatin chemotherapy responding by treatment group and phase

	Akynzeo N=135 %	Palonosetron 0.5 mg N=136 %	p-value
Primary endpoint			
Complete response			
Overall phase[§]	89.6	76.5	0.004
Major secondary endpoints			
Complete response			
Acute phase[‡]	98.5	89.7	0.007
Delayed phase[†]	90.4	80.1	0.018
No emesis			
Acute phase	98.5	89.7	0.007
Delayed phase	91.9	80.1	0.006
Overall phase	91.1	76.5	0.001
No significant nausea			
Acute phase	98.5	93.4	0.050
Delayed phase	90.4	80.9	0.004
Overall phase	89.6	79.4	0.021

[‡]Acute phase: 0 to 24 hours post-cisplatin treatment.
[†]Delayed phase: 25 to 120 hours post-cisplatin treatment.
[§]Overall: 0 to 120 hours post-cisplatin treatment.

Moderately emetogenic chemotherapy (MEC) study
In a multicenter, randomized, parallel, double-blind, active-controlled, superiority study, the efficacy and safety of a single oral dose of Akynzeo was compared with a single oral dose of palonosetron 0.5 mg in cancer patients scheduled to receive the first cycle of an anthracycline and cyclophosphamide regimen for the treatment of a solid malignant tumour. At the time of the study, anthracycline-cyclophosphamide containing chemotherapy regimens were considered to be moderately emetogenic. Recent guidance has updated these regimens to highly emetogenic.
All patients received a single oral dose of dexamethasone.

Table 4: Oral antiemetic treatment regimen – MEC study

Treatment regimen	**Day 1**	**Days 2 to 3**
Akynzeo	Akynzeo Netupitant 300 mg Palonosetron 0.5 mg Dexamethasone 12 mg	No antiemetic treatment
Palonosetron	Palonosetron 0.5 mg Dexamethasone 20 mg	No antiemetic treatment

After completion of cycle 1, patients had the option to participate in a multiple-cycle extension, receiving the same treatment as assigned in cycle 1. There was no pre-specified limit of the number of repeat consecutive cycles for any patient. A total of 1450 patients (Akynzeo n=725; Palonosetron n=725) received study medication. Of these, 1438 patients (98.8%) completed cycle 1 and

1286 patients (88.4%) continued treatment in the multiple-cycle extension. A total of 907 patients (62.3%) completed the multiple-cycle extension up to a maximum of eight treatment cycles.
A total of 724 patients (99.9%) were treated with cyclophosphamide. All patients were additionally treated with either doxorubicin (68.0%) or epirubicin (32.0%).

The primary efficacy endpoint was the CR rate in the delayed phase, 25.120 hours after the start of the chemotherapy administration.

A summary of the key results from this study is shown in Table below.

Table 5: Proportion of patients receiving anthracycline and cyclophosphamide chemotherapy responding by treatment group and phase – cycle 1

	Akynzeo N=724 %	Palonosetron 0.5 mg N=725 %	p-value*
Primary endpoint			
Complete response			
Delayed phase[†]	76.9	69.5	0.001
Major secondary endpoints			
Complete response			
Acute phase[‡]	88.4	85.0	0.047
Overall phase[§]	74.3	66.6	0.001
No emesis			
Acute phase	90.9	87.3	0.025
Delayed phase	81.8	75.6	0.004
Overall phase	79.8	72.1	<0.001
No significant nausea			
Acute phase	87.3	87.9	N.S.
Delayed phase	76.9	71.3	0.014
Overall phase	74.6	69.1	0.020

* p-value from Cochran-Mantel-Haenszel test, stratified by age class and region.
[‡]Acute phase: 0 to 24 hours after anthracycline and cyclophosphamide regimen
[†]Delayed phase: 25 to 120 hours after anthracycline and cyclophosphamide regimen
[§]Overall: 0 to 120 hours after anthracycline and cyclophosphamide regimen

Patients continued into the Multiple-Cycle extension for up to 7 additional cycles of chemotherapy. Antiemetic activity of Akynzeo was maintained throughout repeat cycles for those patients continuing in each of the multiple cycles.
The impact of nausea and vomiting on patients' daily lives was assessed using the Functional Living Index–Emesis (FLIE). The proportion of patients with Overall no impact on daily life was 6.3% higher (p value =0.005) in the Akynzeo group (78.5%) than in the palonosetron group (72.1%).

Multiple-cycle safety study in patients receiving either highly emetogenic chemotherapy or moderately emetogenic chemotherapy
In a separate study, a total of 413 patients undergoing initial and repeat cycles of chemotherapy (including carboplatin, cisplatin, oxaliplatin, and doxorubicin regimens), were randomized to receive either Akynzeo (n=309) or aprepitant and palonosetron (n=104). Safety and efficacy were maintained throughout all cycles.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Akynzeo in all subsets of the paediatric population in prevention of acute and delayed nausea and vomiting associated with highly emetogenic cisplatin-based and moderately emetogenic cancer chemotherapy (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Netupitant
Absolute netupitant bioavailability data are not available in humans; based on data from two studies with intravenous netupitant, the bioavailability in humans is estimated to be greater than 60%.
In single dose oral studies, netupitant was measurable in plasma between 15 minutes and 3 hours after dosing. Plasma concentrations followed a first order absorption process and reached C_{max} in approximately 5 hours. There was a supra-proportional increase in C_{max} and AUC parameters for doses from 10 mg to 300 mg.

In 82 healthy subjects given a single oral dose of netupitant 300 mg, maximum plasma netupitant concentration (C_{max}) was 486 ±268 ng/mL (mean ± SD) and median time to maximum concentration (T_{max}) was 5.25 hours, the AUC was 15032 ± 6858 h.ng/mL. In a pooled analysis, females had a higher netupitant exposure compared to males; there was a 1.31-fold increase in C_{max}, a 1.02 fold increase for AUC and a 1.36 fold increase in half-life.
Netupitant $AUC_{0-\infty}$ and C_{max} increased by 1.1 fold and 1.2 fold, respectively, after a high fat meal.
In 72 healthy subjects single oral doses of Netupitant-Palonosetron oral suspension showed to be bioequivalent with the single administration of the hard capsule with regard to netupitant (AUC_{0-t}: 88.73, 96.19 [% of 90% CI of ratio suspension/capsule]) .

Palonosetron
Following oral administration, palonosetron is well absorbed with its absolute bioavailability reaching 97%. After single oral doses using buffered solution mean maximum palonosetron concentrations (C_{max}) and area under the concentration-time curve ($AUC_{0-\infty}$) were dose proportional over the dose range of 3.0 to 80 mcg/kg in healthy subjects.

In 36 healthy male and female subjects given a single oral dose of 0.5 mg palonosetron, maximum plasma concentration (C_{max}) was 0.81 ± 1.66 ng/mL (mean ± SD) and time to maximum concentration (T_{max}) was 5.1 ± 1.7 hours. In female subjects (n=18), the mean AUC was 35% higher and the mean C_{max} was 26% higher than in male subjects (n=18). In 12 cancer patients given a single oral dose of palonosetron 0.5 mg one hour prior to chemotherapy, C_{max} was 0.93 ± 0.34 ng/mL and T_{max} was 5.1 ± 5.9 hours. The AUC was 30% higher in cancer patients than in healthy subjects. A high fat meal did not affect the C_{max} and AUC of oral palonosetron.

In 72 healthy subjects single oral doses of Netupitant-Palonosetron oral suspension showed to be bioequivalent with the single administration of the hard capsule with regard to palonosetron (AUC_{0-t}: 97.42, 101.28 [% of 90% CI of ratio suspension/capsule]).

Distribution

Netupitant
After a single oral 300 mg dose administration in cancer patients, netupitant disposition was characterised by a two compartment model with an estimated median systemic clearance of 20.5 L/h and a large distribution volume in the central compartment (486 L). Human plasma protein binding of netupitant and its two major metabolites M1 and M3 is > 99% at concentrations ranging from 10 to 1500 ng/mL. The third major metabolite, M2, is > 97% bound to plasma proteins.

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

Biotransformation

Netupitant
Three metabolites have been detected in human plasma at netupitant oral doses of 30 mg and higher (the desmethyl derivative, M1; the N-oxide derivative, M2; the OH-methyl derivative, M3). *In vitro* metabolism studies have suggested that CYP3A4 and, to a lesser extent, CYP2D6 and CYP2C9 are involved in the metabolism of netupitant. After administration of a single oral dose of 300 mg netupitant, mean plasma netupitant/plasma radioactivity ratios ranged from 0.13 to 0.49 over 96 h post-dose. The ratios were time dependent with values decreasing gradually beyond 24 h post-dose, indicating that netupitant is being rapidly metabolised. Mean C_{max} was approximately 11%, 47% and 16% of the parent for M1, M2 and M3 respectively; M2 had the lowest AUC relative to the parent (14%) whereas M1 and M3 AUC were approximately 29% and 33% of the parent, respectively. M1, M2 and M3 metabolites were all shown to be pharmacologically active in an animal pharmacodynamic model, where M3 was most potent and M2 least active.

Palonosetron
Palonosetron is eliminated by multiple routes with approximately 50% metabolised to form two primary metabolites: N-oxide-palonosetron and 6-S-hydroxy-palonosetron. These metabolites each have less than 1% of the 5-HT_3 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

Netupitant
Following administration of a single dose of Akynzeo, netupitant is eliminated from the body in a multi-exponential fashion, with an apparent mean elimination half-life of 88 hours in cancer patients. Renal clearance is not a significant elimination route for netupitant-related entities. The mean fraction of an oral dose of netupitant excreted unchanged in urine is less than 1%; a total of 3.95% and 70.7% of the radioactive dose was recovered in the urine and faeces, respectively. Approximately half the radioactivity administered orally as [14C]-netupitant was recovered from urine and faeces within 120 h of dosing. Elimination via both routes was estimated to be complete by Day 29-30 post-dose.

Palonosetron
Following administration of a single oral 0.75 mg dose of [14C]-palonosetron to six healthy subjects, 85% to 93% of the total radioactivity was excreted in urine, and 5% to 8% was eliminated in faeces. The amount of unchanged palonosetron excreted in the urine represented approximately 40% of the administered dose. In healthy subjects given palonosetron capsules 0.5 mg, the terminal elimination half-life (t½) of palonosetron was 37 ± 12 hours (mean ± SD), and in cancer patients, t½ was 48 ± 19 hours. After a single dose of approximately 0.75 mg intravenous palonosetron, the total body clearance of palonosetron in healthy subjects was 160 ± 35 mL/h/kg (mean ± SD) and renal clearance was 66.5± 18.2 mL/h/kg.

Special populations

Hepatic impairment

Netupitant
Maximum concentrations and total exposure of netupitant were increased in subjects with mild (n=8), moderate (n=8), and severe (n=2) hepatic impairment compared to matching healthy subjects,

although there was pronounced individual variability in both hepatically-impaired and healthy subjects. Exposure to netupitant (C_{max}, AUC_{0-t} and $AUC_{0-\infty}$) compared to matching healthy subjects was 11%, 28% and 19% higher in mild and 70%, 88% and 143% higher in moderate hepatically-impaired subjects, respectively. As such, no dose adjustment is necessary for patients with mild to moderate hepatic impairment. Limited data exist in patients with severe hepatic impairment (Child Pugh score ≥9).

Palonosetron
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.

Renal impairment

Netupitant
No specific studies were performed to evaluate netupitant in patients with renal impairment. In the ADME trial, less than 5% of all netupitant-related material was excreted in urine and less than 1% of the netupitant dose was eliminated unchanged in the urine and therefore any accumulation of netupitant or metabolites after a single dose would be negligible. Furthermore, the population PK study showed no correlation between PK parameters of netupitant and markers of renal dysfunction.

Palonosetron
Mild to moderate renal impairment does not significantly affect palonosetron PK parameters. Total systemic exposure to intravenous palonosetron increased by approximately 28% in patients with severe impairment relative to healthy subjects. In a population PK study, patients with a reduced creatinine clearance (CL_{CR}) also had a reduced palonosetron clearance, but this reduction would not result in a significant change in palonosetron exposure.

Therefore, Akynzeo can be administered without dose adjustment in patients with renal impairment.

Neither netupitant nor palonosetron have been evaluated in patients with end-stage renal disease.

5.3 Preclinical safety data

Palonosetron

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. Degeneration of seminiferous epithelium was associated with palonosetron following a one month oral repeat dose toxicity study in rats. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. Only limited data from animal studies are available regarding the placental transfer (see section 4.6). Palonosetron is not mutagenic. High doses of palonosetron (each dose causing at least 15 times the human therapeutic exposure) applied daily for two years caused an increased rate of liver tumours, endocrine neoplasms (in thyroid, pituitary, pancreas, adrenal medulla) and skin tumours in rats but not in mice. The underlying mechanisms are not fully understood, but because of the high doses employed and since the medicinal product is intended for single application in humans, these findings are not considered relevant for clinical use.

Netupitant and combination with palonosetron

Effects in non-clinical studies based on safety pharmacology and single and repeated dose toxicity were observed only at exposures considered in excess of the maximum human exposure, indicating little relevance to clinical use. Phospholipidosis (foamy macrophages) has been observed with the

administration of netupitant after repeated administration in rats and dogs. The effects were reversible or partially reversible after the recovery period. The significance of these findings in humans is unknown.

Non-clinical studies indicate that netupitant and its metabolites and the combination with palonosetron only at very high concentrations may block ion channels involved in ventricular de- and re-polarisation and prolong action potential duration. Reproductive studies in animals with netupitant do not indicate direct or indirect harmful effects with respect to fertility, parturition or postnatal development. An increased incidence of positional foetal abnormalities of the limbs and paws, fused sternebrae and agenesis of accessory lung lobe were observed following daily administration of netupitant in rabbits at 10 mg/kg/day and higher during the period of organogenesis. In a pilot dose range finding study in rabbits, cleft palate, microphtalmia and aphakia were observed in four foetuses from one litter in the 30 mg/kg/day group. The relevance of these findings in humans is unknown. No data from animal studies with netupitant are available regarding placental transfer and lactation. Netupitant is not mutagenic.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycerol (E 422)
Xanthan gum
Citric acid
Sodium citrate dihydrate
Potassium sorbate
Sorbitol, liquid (non-crystallising) (E 420)
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

10 ml PET/ALU/PE sachet (Polyester/Aluminium/Polyethylene).

Available in a pack size of 1 or 4 single sachets packaged in a single unit outer carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Helsinn Birex Pharmaceuticals Ltd.
Damastown

Mulhuddart
Dublin 15
Ireland.

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1001/005
EU/1/15/1001/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27 May 2015
Date of latest renewal: 12 February 2026

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Helsinn Birex Pharmaceuticals Ltd.
Damastown,
Mulhuddart
Dublin 15
Ireland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

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

Akynzeo 300 mg/0.5 mg hard capsules
netupitant/palonosetron

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 300 milligrams of netupitant and 0.5 milligrams of palonosetron (as hydrochloride).

3. LIST OF EXCIPIENTS

Contains sucrose and sorbitol (E420). See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule

1 hard capsule
4x1 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1001/001 1 hard capsule
EU/1/15/1001/002 4x1 hard capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

akynzeo

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Akynzeo 300 mg/0.5 mg hard capsules
netupitant/palonosetron

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Helsinn

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Akynzeo 235 mg/0.25 mg powder for concentrate for solution for infusion
fosnetupitant/palonosetron

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 235 mg of fosnetupitant (as chloride hydrochloride), which corresponds to 197.5 mg of netupitant, and 0.25 mg of palonosetron (as hydrochloride).

After reconstitution and dilution, 1 ml of solution contains 4.7 mg fosnetupitant, which corresponds to 3.95 mg of netupitant, and 0.005 mg palonosetron.

3. LIST OF EXCIPIENTS

Also contains mannitol, disodium edetate, sodium hydroxide and hydrochloric acid.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for infusion

1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use after reconstitution and dilution.
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

Store in a refrigerator. Keep the vial in the outer carton in order to protect from light.
After reconstitution and dilution: 24 hours below 25°C.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Helsinn Birex Pharmaceuticals Ltd.
Damastown
Mulhuddart
Dublin 15
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1001/003

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

PARTICULARS TO APPEAR THE IMMEDIATE PACKAGING
VIAL

1. NAME OF THE MEDICINAL PRODUCT

Akynzeo 235 mg/0.25 mg powder for concentrate for solution for infusion
fosnetupitant/palonosetron

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 235 mg of fosnetupitant (as chloride hydrochloride), which corresponds to 197.5 mg of netupitant, and 0.25 mg of palonosetron (as hydrochloride).

After reconstitution and dilution, 1 ml of solution contains 4.7 mg fosnetupitant, which corresponds to 3.95 mg of netupitant, and 0.005 mg palonosetron.

3. LIST OF EXCIPIENTS

Also contains mannitol, disodium edetate, sodium hydroxide and hydrochloric acid.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for infusion

1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
IV use after reconstitution and dilution
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

Store in a refrigerator. Keep the vial in the outer carton in order to protect from light.
After reconstitution and dilution: 24 hours below 25°C

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Helsinn Birex Pharmaceuticals Ltd.
Damastown
Mulhuddart
Dublin 15
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1001/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Akynzeo 235 mg/0.25 mg concentrate for solution for infusion
fosnetupitant/palonosetron

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial of 20 ml contains 235 mg of fosnetupitant (as chloride hydrochloride), which corresponds to 197.5 mg of netupitant, and 0.25 mg of palonosetron (as hydrochloride).
Each ml of concentrate for solution contains 11.75 mg fosnetupitant, which corresponds to 9.87 mg of netupitant, and 0.0125 mg palonosetron

After dilution, 1 ml of solution contains 4.7 mg fosnetupitant, which corresponds to 3.95 mg of netupitant, and 0.005 mg palonosetron.

3. LIST OF EXCIPIENTS

Also contains mannitol, disodium edetate, sodium hydroxide, hydrochloric acid and water.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion

1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use after dilution.
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

Store below 25°C. Keep the vial in the outer carton in order to protect from light.
After dilution: 24 hours below 25°C.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Helsinn Birex Pharmaceuticals Ltd.
Damastown
Mulhuddart
Dublin 15
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1001/004

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

PARTICULARS TO APPEAR THE IMMEDIATE PACKAGING
VIAL

1. NAME OF THE MEDICINAL PRODUCT

Akynzeo 235 mg/0.25 mg concentrate for solution for infusion
fosnetupitant/palonosetron

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial of 20 ml contains 235 mg of fosnetupitant (as chloride hydrochloride), which corresponds to 197.5 mg of netupitant, and 0.25 mg of palonosetron (as hydrochloride).
Each ml of concentrate for solution contains 11.75 mg fosnetupitant, which corresponds to 9.87 mg of netupitant, and 0.0125 mg palonosetron

After dilution, 1 ml of solution contains 4.7 mg fosnetupitant, which corresponds to 3.95 mg of netupitant, and 0.005 mg palonosetron.

3. LIST OF EXCIPIENTS

Also contains mannitol, disodium edetate, sodium hydroxide, hydrochloric acid and water.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion

1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use after dilution
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

Store below 25°C. Keep the vial in the outer carton in order to protect from light.
After dilution: 24 hours below 25°C

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Helsinn Birex Pharmaceuticals Ltd.
Damastown
Mulhuddart
Dublin 15
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1001/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Akynzeo 300 mg/0.5 mg oral suspension in sachet
netupitant/palonosetron

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each sachet contains 300 milligrams of netupitant and 0.5 milligrams of palonosetron (as hydrochloride).

3. LIST OF EXCIPIENTS

Contains sodium, potassium and sorbitol (E420). See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Oral suspension

1 sachet
4 sachets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1001/005 1 sachet
EU/1/15/1001/006 4 x 1 sachets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

akynzeo oral suspension

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

SACHET

1. NAME OF THE MEDICINAL PRODUCT

Akynzeo 300 mg/0.5 mg oral suspension in sachet
netupitant/palonosetron

2. METHOD OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 ml

6. OTHER

B. PACKAGE LEAFLET

Package Leaflet: Information for the patient

Akynzeo 300 mg/0.5 mg hard capsules
netupitant/palonosetron

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

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

What is in this leaflet

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

1. What Akynzeo is and what it is used for

What Akynzeo is
Akynzeo contains two active substances called:
- netupitant
- palonosetron.

What Akynzeo is used for
Akynzeo is used to help prevent adults with cancer feeling sick (nausea) or being sick (vomiting) while having cancer treatment called 'chemotherapy'.

How Akynzeo works
Chemotherapy medicines can cause the body to release substances called serotonin and substance P. This stimulates the vomiting centre in the brain, making you feel or be sick. The medicines in Akynzeo attach to the receptors in the nervous system through which serotonin and substance P work: netupitant (an NK_1 receptor antagonist) blocks the receptors for substance P, and palonosetron (a 5-HT_3 receptor antagonist) blocks certain receptors for serotonin. By blocking the actions of substance P and serotonin in this way, the medicines help prevent the stimulation of the vomiting centre and the resulting sickness.

2. What you need to know before you take Akynzeo

Do not take Akynzeo if:
- you are allergic to netupitant or palonosetron, or any of the other ingredients of this medicine (listed in section 6). If you are not sure, talk to your doctor, pharmacist or nurse before taking this medicine.
- you are pregnant.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before taking Akynzeo if:
- you have liver problems
- you have a blockage in your gut, or you have had constipation in the past
- you or one of your close relatives has ever had a heart problem called 'QT interval prolongation'
- you have any other heart problems
- you have been told you have an imbalance of minerals in your blood such as potassium and magnesium that has not been corrected.

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

Children and adolescents
Akynzeo should not be taken by children and adolescents under 18 years.

Other medicines and Akynzeo
Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines.

In particular tell your doctor, pharmacist or nurse if you are taking any of the following medicines:
- medicines for depression or anxiety called SSRIs (selective serotonin re-uptake inhibitors) - such as fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram or escitalopram
- medicines for depression or anxiety called SNRIs (serotonin noradrenaline re-uptake inhibitors) - such as venlafaxine or duloxetine.

Also tell your doctor, pharmacist or nurse if you are taking any of the following medicines as your doctor may need to change the dose of these other medicines:
- medicines that might cause abnormal heartbeat such as amiodarone, nicardipine, quinidine, moxifloxacin, haloperidol, chlorpromazine, quetiapine, thioridazine or domperidone
- medicines with a narrow therapeutic range that are primarily metabolised by CYP3A4, such as cyclosporine, tacrolimus, sirolimus, everolimus, alfentanil, diergotamine, ergotamine, fentanyl, or quinidine
- some chemotherapy medicines - such as docetaxel or etoposide
- erythromycin - to treat bacterial infections
- midazolam - a sedative used to treat anxiety
- dexamethasone - can be used to treat feeling and being sick
- ketoconazole - to treat Cushing's syndrome
- rifampicin - to treat tuberculosis (TB) and other infections.

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

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Do not take Akynzeo if you are pregnant or if you are a woman of childbearing potential not using contraception.

Do not breast-feed if you are taking Akynzeo. This is because it is not known whether the medicine passes into breast milk.

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

Akynzeo contains sucrose, sorbitol (E420), sodium and may contain traces of soya
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

This medicine contains 7 mg of sorbitol (E420) in each hard capsule.

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

It may contain traces of lecithin - which comes from soya. If you are allergic to peanut or soya, do not use this medicinal product.

3. How to take Akynzeo

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

How much to take
- The recommended dose is one capsule (each capsule contains 300 mg of netupitant and 0.5 mg of palonosetron).
- Take the capsule about 1 hour before you start your chemotherapy cycle.
- You can take Akynzeo with or without food.

Akynzeo is taken before the chemotherapy to prevent sickness and feelings of sickness from developing. Do not take Akynzeo in the days after you have chemotherapy - unless you are about to have another chemotherapy cycle.

If you take more Akynzeo than you should
The usual dose is 1 capsule. If you think you may have taken more than you should, tell your doctor straight away. The symptoms of overdose may include headache, dizziness, constipation, anxiety, palpitations, euphoric mood and pain in the legs.

If you forget to take Akynzeo
If you think you have forgotten to take your dose, tell your doctor straight away.

If you stop taking Akynzeo
Akynzeo is taken to help prevent you feeling and being sick when you are having chemotherapy. If you do not want to take Akynzeo, discuss this with your doctor. If you decide not to take Akynzeo (or another similar medicine), your chemotherapy is likely to make you feel sick and be sick.

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

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects
Stop taking Akynzeo and tell your doctor straight away if you notice the following serious side effect - you may need urgent medical treatment:

Very rare: may affect up to 1 in 10,000 people
- severe allergic reaction signs include hives, skin rash, itching, difficulty breathing or swallowing, swollen mouth, face, lips, tongue or throat and sometimes a drop in blood pressure.

Other side effects

Tell your doctor, pharmacist or nurse if you notice any of the following side effects:

Common: (may affect up to 1 in 10 people)
- headache
- constipation
- feeling tired.

Uncommon: (may affect up to 1 in 100 people)
- hair loss
- lack of energy (feeling weak)
- decreased appetite
- high blood pressure
- raised, itchy rash on the skin (hives)
- problems with the muscles in your heart (cardiomyopathy)
- spinning sensation (vertigo), feeling dizzy or trouble sleeping (insomnia)
- stomach problems including stomach discomfort, feeling bloated, nausea, pain, indigestion, hiccups, wind or diarrhoea
- high levels of certain enzymes, including blood alkaline phosphatase and liver transaminases (shown in blood tests)
- high levels of creatinine - which measures kidney function (shown in blood tests)
- ECG (electrocardiogram) problems (called 'QT and PR interval prolongation', 'conduction disorder', 'tachycardia' and 'atrioventricular block first degree')
- low levels of 'neutrophils' - a kind of white blood cell which fight infections (shown in blood tests)
- high level of white blood cells (shown in blood tests).

Rare: (may affect up to 1 in 1 000 people)
- back pain, joint pain
- feeling hot, reddening of the face or other areas of the skin (feeling flushed)
- itchy skin rash
- feeling drowsy
- sleep problems
- ring in the ear
- vomiting
- low blood pressure
- chest pain (not related to the heart)
- numbness, blurred vision
- sudden nervous breakdown, change in mood
- infection and inflammation in the bladder (cystitis)
- haemorrhoids
- conjunctivitis (a type of eye inflammation)
- low level of potassium (shown in blood tests)
- modifications (or disturbances) in heart rhythm
- heart valve disorder (mitral valve incompetence)
- coating of the tongue, difficulty swallowing, dry mouth, belching, abnormal taste after medicine intake
- decreased blood flow to the heart muscle (myocardial ischemia)
- high levels of creatine phosphokinase/ creatine phosphokinase MB - which indicates sudden decreased blood flow to the heart muscle (shown in blood tests)
- high levels of troponin - which indicates heart muscle dysfunction (shown in blood tests)
- high levels of the pigment bilirubin - which indicates liver dysfunction (shown in blood tests)
- high levels of myoglobin – which indicates muscle injury (shown in blood tests)
- high levels of blood urea – which indicates kidney dysfunction (shown in blood tests)

- high level of 'lymphocytes'– type of white blood cell which help the body fight disease (shown in blood tests)
- low level of white blood cells (shown in blood tests)
- ECG (electrocardiogram) problems (called 'ST segment depression', 'ST-T segment abnormal' 'bundle branch block right/left', and 'atrioventricular block second degree')

Reporting of side effects
If you get any side effects, talk to your doctor, 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 Akynzeo

- 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 blister after 'EXP'. The expiry date refers to the last day of that month.
- This medicine does not require any special storage conditions.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Akynzeo contains
- The active substances are palonosetron and netupitant. Each hard capsule contains three tablets (300 mg of netupitant), and one soft capsule (palonosetron hydrochloride equivalent to 0.5 milligrams of palonosetron).
- The other ingredients are microcrystalline cellulose (E460), sucrose lauric acid esters, povidone K-30, croscarmellose sodium, colloidal hydrated silica, sodium stearyl fumarate, magnesium stearate, glycerol monocaprylocaproate (type I), glycerol, polyglyceryl oleate, purified water, butylhydroxyanisole (E320), gelatin, sorbitol (E420), 1,4 sorbitan, titanium dioxide (E171), shellac glaze (partially esterified), yellow, red and black iron oxide (E172), propylene glycol (E1520).

This medicine contains sucrose, sorbitol (E420), sodium and may contain soya - see section 2 for more information.

What Akynzeo looks like and contents of the pack
The hard capsules are opaque with a white body and a caramel cap with 'HE1' printed on the body. Pack size containing 1 capsule in an aluminium blister or 4 x 1 hard capsules in aluminium perforated unit dose blisters. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer:
Helsinn Birex Pharmaceuticals Ltd.
Damastown
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This leaflet was last revised in

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

Package Leaflet: Information for the patient

Akynzeo 235 mg/0.25 mg powder for concentrate for solution for infusion
fosnetupitant/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, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

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

1. What Akynzeo is and what it is used for

What Akynzeo is
Akynzeo contains two active substances called:
- fosnetupitant
- palonosetron.

What Akynzeo is used for
Akynzeo is used to help prevent adults with cancer feeling sick (nausea) or being sick (vomiting) while having cancer treatment called 'chemotherapy'.

How Akynzeo works
Chemotherapy medicines can cause the body to release substances called serotonin and substance P. This stimulates the vomiting centre in the brain, making you feel or be sick. The medicines in Akynzeo attach to the receptors in the nervous system through which serotonin and substance P work: fosnetupitant which is converted to netupitant (an NK_1 receptor antagonist) in your body blocks the receptors for substance P, and palonosetron (a 5-HT_3 receptor antagonist) blocks certain receptors for serotonin. By blocking the actions of substance P and serotonin in this way, the medicines help prevent the stimulation of the vomiting centre and the resulting sickness.

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

You should not be given Akynzeo if:
- you are allergic to fosnetupitant, netupitant or palonosetron, or any of the other ingredients of this medicine (listed in section 6). If you are not sure, talk to your doctor, pharmacist or nurse before you are given this medicine.
- you are pregnant.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before being given Akynzeo if:

- you have liver problems
- you have a blockage in your gut or you have had constipation in the past
- you or one of your close relatives has ever had a heart problem called 'QT interval prolongation'
- you have any other heart problems
- you have been told you have an imbalance of minerals in your blood such as potassium and magnesium that has not been corrected.

If any of the above apply to you (or you are not sure), talk to your doctor, pharmacist or nurse before being given Akynzeo.

Children and adolescents
Akynzeo should not be given to children and adolescents under 18 years.

Other medicines and Akynzeo
Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines.

In particular tell your doctor, pharmacist or nurse if you are taking any of the following medicines:
- medicines for depression or anxiety called SSRIs (selective serotonin re-uptake inhibitors) - such as fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram or escitalopram
- medicines for depression or anxiety called SNRIs (serotonin noradrenaline re-uptake inhibitors) - such as venlafaxine or duloxetine.

Also tell your doctor, pharmacist or nurse if you are taking any of the following medicines as your doctor may need to change the dose of these other medicines:
- medicines that might cause abnormal heartbeat such as amiodarone, nicardipine, quinidine, moxifloxacin, haloperidol, chlorpromazine, quetiapine, thioridazine or domperidone
- medicines with a narrow therapeutic range that are primarily metabolised by CYP3A4, such as cyclosporine, tacrolimus, sirolimus, everolimus, alfentanil, diergotamine, ergotamine, fentanyl, or quinidine
- some chemotherapy medicines - such as docetaxel or etoposide
- erythromycin - to treat bacterial infections
- midazolam - a sedative used to treat anxiety
- dexamethasone - can be used to treat feeling and being sick
- ketoconazole - to treat Cushing's syndrome
- rifampicin - to treat tuberculosis (TB) and other infections.

If any of the above apply to you (or you are not sure), talk to your doctor, pharmacist or nurse before being given Akynzeo.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before being given this medicine.

You should not be given Akynzeo if you are pregnant or if you are a woman of childbearing potential not using contraception.

Do not breast-feed if you are being given Akynzeo. This is because it is not known whether the medicine passes into breast milk.

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

Akynzeo contains sodium
This medicine contains 24.8 mg sodium (main component of cooking/table salt) in each vial. This is equivalent to 1.24% of the recommended maximum daily dietary intake of sodium for an adult.
If reconstituted and diluted with sodium chloride 9 mg/ml (0.9%) solution for injection, the final solution contains approximately 202 mg of sodium per dose. This is equivalent to 10.1% of the recommended maximum daily dietary intake of sodium for an adult.

3. How Akynzeo is given

The recommended dose of Akynzeo is one vial (each vial contains 235 mg of fosnetupitant and 0.25 mg of palonosetron) on Day 1 of your chemotherapy.
- The powder is reconstituted and diluted before use.
- Akynzeo is given to you by a doctor or nurse
- Akynzeo is given as a drip into a vein (intravenous infusion) about 30 minutes before you start your chemotherapy treatment.

Your doctor will ask you to take other medicines including a corticosteroid (such as dexamethasone) to prevent you feeling and being sick. Check with your doctor or nurse if you are not sure.

If you stop being given Akynzeo
Akynzeo is given to help prevent you feeling and being sick when you are having chemotherapy. If you do not want to be given Akynzeo, discuss this with your doctor. If you decide not to be given Akynzeo (or another similar medicine), your chemotherapy is likely to make you feel and be sick.

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

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects
Stop being given Akynzeo and tell your doctor straight away if you notice the following serious side effect - you may need urgent medical treatment:

Very rare (may affect up to 1 in 10 000 people)
- severe allergic reaction – signs include hives, skin rash, itching, difficulty breathing or swallowing, swollen mouth, face, lips, tongue or throat and sometimes a drop in blood pressure.

Other side effects
Tell your doctor, pharmacist or nurse if you notice any of the following side effects:

Common (may affect up to 1 in 10 people)
- headache
- constipation
- feeling tired.

Uncommon (may affect up to 1 in 100 people)
- hair loss
- lack of energy (feeling weak)
- decreased appetite
- high blood pressure
- raised, itchy rash on the skin (hives)
- problems with the muscles in your heart (cardiomyopathy)
- spinning sensation (vertigo), feeling dizzy or trouble sleeping (insomnia)

- stomach problems including stomach discomfort, feeling bloated, nausea, pain, indigestion, hiccups, wind or diarrhoea
- high levels of certain enzymes, including blood alkaline phosphatase and liver transaminases (shown in blood tests)
- high levels of creatinine - which measures kidney function (shown in blood tests)
- ECG (electrocardiogram) problems (called 'QT and PR interval prolongation', 'conduction disorder', 'tachycardia' and 'atrioventricular block first degree')
- low levels of 'neutrophils' - a kind of white blood cell which fight infections (shown in blood tests)
- high level of white blood cells (shown in blood tests).

Rare (may affect up to 1 in 1 000 people)
- back pain, joint pain
- feeling hot, reddening of the face or other areas of the skin (feeling flushed)
- itchy skin rash
- feeling drowsy
- sleep problems
- ring in the ear
- vomiting
- low blood pressure
- chest pain (not related to the heart)
- numbness, blurred vision
- sudden nervous breakdown, change in mood
- infection and inflammation in the bladder (cystitis)
- haemorrhoids
- conjunctivitis (a type of eye inflammation)
- low level of potassium (shown in blood tests)
- modifications (or disturbances) in heart rhythm
- heart valve disorder (mitral valve incompetence)
- coating of the tongue, difficulty swallowing, dry mouth, belching, abnormal taste after medicine intake
- decreased blood flow to the heart muscle (myocardial ischemia)
- high levels of creatine phosphokinase//creatine phosphokinase MB - which indicates sudden decreased blood flow to the heart muscle (shown in blood tests)
- high levels of troponin - which indicates heart muscle dysfunction (shown in blood tests)
- high levels of the pigment bilirubin - which indicates liver dysfunction (shown in blood tests)
- high levels of myoglobin – which indicates muscle injury (shown in blood tests)
- high levels of blood urea – which indicates kidney dysfunction (shown in blood tests)
- high level of 'lymphocytes'– type of white blood cell which help the body fight disease (shown in blood tests)
- low level of white blood cells (shown in blood tests)
- ECG (electrocardiogram) problems (called 'ST segment depression', 'ST-T segment abnormal' 'bundle branch block right/left', and 'atrioventricular block second degree')

Reporting of side effects
If you get any side effects, talk to your doctor, 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 Akynzeo

- 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 vial after 'EXP'. The expiry date refers to the last day of that month.
- Store in a refrigerator (2°C – 8°C).
- Keep the vial in the outer carton in order to protect from light.
- The total time from reconstitution to the start of the infusion should not exceed 24 hours. Store the reconstituted solution and the final diluted solution below 25°C.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Akynzeo contains
- The active substances are fosnetupitant and palonosetron. Each vial contains 235 mg of fosnetupitant and 0.25 milligrams of palonosetron.
- The other ingredients are mannitol, disodium edetate (E386), sodium hydroxide (E524), hydrochloric acid diluted (E507) (for pH adjustment).

This medicine contains sodium, see section 2 for more information.

What Akynzeo looks like and contents of the pack
Akynzeo powder for concentrate for solution for infusion is a sterile, white to off-white lyophilised powder and is supplied in a pack of one Type I glass vial with rubber stopper and aluminium cap. Each vial contains one dose.

Pack of 1 vial.

Marketing Authorisation Holder and Manufacturer:
Helsinn Birex Pharmaceuticals Ltd.
Damastown
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in

Other sources of information

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

The following information is intended for medical or healthcare professionals only:

Instructions of how to reconstitute and dilute AKYNZEO 235 mg/0.25 mg

Preparation of Akynzeo

Step 1	Aseptically inject 20 mL 5% glucose injection or sodium chloride 9 mg/ml (0.9%) solution for injection, into the vial. Ensure the solvent is added to the vial along the vial wall and not jetted in order to prevent foaming. Swirl the vial gently for 3 minutes. The powder should be dissolved before the solution is diluted in the infusion bag.
Step 2	Aseptically prepare an infusion vial or bag filled with 30 mL of 5% glucose injection, or sodium chloride 9 mg/ml (0.9%) solution for injection.
Step 3	Dilution should occur immediately after reconstitution (according to Step 1). Aseptically withdraw the entire volume of reconstituted solution from the AKYNZEO vial and transfer it into the infusion vial or bag containing 30 mL of 5% glucose injection or sodium chloride 9 mg/ml (0.9%) solution for injection to yield a total volume of 50 mL.
Step 4	Gently invert the vial or bag until complete dissolution.
Step 5	Before administration, inspect the final diluted solution for particulate matter and discolouration. Discard the vial or bag if particulates and/or discolouration are observed.

The reconstituted and diluted final solution is stable for 24 hours at 25°C.

Parenteral medicines should be inspected visually for particulate matter and discolouration before administration whenever solution and container permit.

The appearance of the reconstituted solution is the same as the appearance of the diluent.

Discard any remaining solution and waste material. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

The medicinal product must not be reconstituted or mixed with solutions for which physical and chemical compatibility has not been established (see Summary of Product Characteristic (SmPC), section 6.2).

Package Leaflet: Information for the patient

Akynzeo 235 mg/0.25 mg concentrate for solution for infusion
fosnetupitant/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, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

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

1. What Akynzeo is and what it is used for

What Akynzeo is
Akynzeo contains two active substances called:
- fosnetupitant
- palonosetron.

What Akynzeo is used for
Akynzeo is used to help prevent adults with cancer feeling sick (nausea) or being sick (vomiting) while having cancer treatment called 'chemotherapy'.

How Akynzeo works
Chemotherapy medicines can cause the body to release substances called serotonin and substance P. This stimulates the vomiting centre in the brain, making you feel or be sick. The medicines in Akynzeo attach to the receptors in the nervous system through which serotonin and substance P work: fosnetupitant which is converted to netupitant (an NK_1 receptor antagonist) in your body blocks the receptors for substance P, and palonosetron (a 5-HT_3 receptor antagonist) blocks certain receptors for serotonin. By blocking the actions of substance P and serotonin in this way, the medicines help prevent the stimulation of the vomiting centre and the resulting sickness.

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

You should not be given Akynzeo if:
- you are allergic to fosnetupitant, netupitant or palonosetron, or any of the other ingredients of this medicine (listed in section 6). If you are not sure, talk to your doctor, pharmacist or nurse before you are given this medicine.
- you are pregnant.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before being given Akynzeo if:

- you have liver problems
- you have a blockage in your gut or you have had constipation in the past
- you or one of your close relatives has ever had a heart problem called 'QT interval prolongation'
- you have any other heart problems
- you have been told you have an imbalance of minerals in your blood such as potassium and magnesium that has not been corrected.

If any of the above apply to you (or you are not sure), talk to your doctor, pharmacist or nurse before being given Akynzeo.

Children and adolescents
Akynzeo should not be given to children and adolescents under 18 years.

Other medicines and Akynzeo
Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines.

In particular tell your doctor, pharmacist or nurse if you are taking any of the following medicines:
- medicines for depression or anxiety called SSRIs (selective serotonin re-uptake inhibitors) - such as fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram or escitalopram
- medicines for depression or anxiety called SNRIs (serotonin noradrenaline re-uptake inhibitors) - such as venlafaxine or duloxetine.

Also tell your doctor, pharmacist or nurse if you are taking any of the following medicines as your doctor may need to change the dose of these other medicines:
- medicines that might cause abnormal heartbeat such as amiodarone, nicardipine, quinidine, moxifloxacin, haloperidol, chlorpromazine, quetiapine, thioridazine or domperidone
- medicines with a narrow therapeutic range that are primarily metabolised by CYP3A4, such as cyclosporine, tacrolimus, sirolimus, everolimus, alfentanil, diergotamine, ergotamine, fentanyl, or quinidine
- some chemotherapy medicines - such as docetaxel or etoposide
- erythromycin - to treat bacterial infections
- midazolam - a sedative used to treat anxiety
- dexamethasone - can be used to treat feeling and being sick
- ketoconazole - to treat Cushing's syndrome
- rifampicin - to treat tuberculosis (TB) and other infections.

If any of the above apply to you (or you are not sure), talk to your doctor, pharmacist or nurse before being given Akynzeo.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before being given this medicine.

You should not be given Akynzeo if you are pregnant or if you are a woman of childbearing potential not using contraception.

Do not breast-feed if you are being given Akynzeo. This is because it is not known whether the medicine passes into breast milk.

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

Akynzeo contains sodium
This medicine contains 24.4 mg sodium (main component of cooking/table salt) in each vial. This is equivalent to 1.22% of the recommended maximum daily dietary intake of sodium for an adult.
If diluted with sodium chloride 9 mg/ml (0.9%) solution for injection, the final solution contains approximately 202 mg of sodium per dose. This is equivalent to 10.1% of the recommended maximum daily dietary intake of sodium for an adult.

3. How Akynzeo is given

The recommended dose of Akynzeo is one vial (each vial contains 235 mg of fosnetupitant and 0.25 mg of palonosetron) on Day 1 of your chemotherapy.
- The concentrate is diluted before use.
- Akynzeo is given to you by a doctor or nurse
- Akynzeo is given as a drip into a vein (intravenous infusion) about 30 minutes before you start your chemotherapy treatment.

Your doctor will ask you to take other medicines including a corticosteroid (such as dexamethasone) to prevent you feeling and being sick. Check with your doctor or nurse if you are not sure.

If you stop being given Akynzeo
Akynzeo is given to help prevent you feeling and being sick when you are having chemotherapy. If you do not want to be given Akynzeo, discuss this with your doctor. If you decide not to be given Akynzeo (or another similar medicine), your chemotherapy is likely to make you feel and be sick.

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

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects
Stop being given Akynzeo and tell your doctor straight away if you notice the following serious side effect - you may need urgent medical treatment:

Very rare (may affect up to 1 in 10 000 people)
- severe allergic reaction – signs include hives, skin rash, itching, difficulty breathing or swallowing, swollen mouth, face, lips, tongue or throat and sometimes a drop in blood pressure.

Other side effects
Tell your doctor, pharmacist or nurse if you notice any of the following side effects:

Common (may affect up to 1 in 10 people)
- headache
- constipation
- feeling tired.

Uncommon (may affect up to 1 in 100 people)
- hair loss
- lack of energy (feeling weak)
- decreased appetite
- high blood pressure
- raised, itchy rash on the skin (hives)
- problems with the muscles in your heart (cardiomyopathy)
- spinning sensation (vertigo), feeling dizzy or trouble sleeping (insomnia)

- stomach problems including stomach discomfort, feeling bloated, nausea, pain, indigestion, hiccups, wind or diarrhoea
- high levels of certain enzymes, including blood alkaline phosphatase and liver transaminases (shown in blood tests)
- high levels of creatinine - which measures kidney function (shown in blood tests)
- ECG (electrocardiogram) problems (called 'QT and PR interval prolongation', 'conduction disorder', 'tachycardia' and 'atrioventricular block first degree')
- low levels of 'neutrophils' - a kind of white blood cell which fight infections (shown in blood tests)
- high level of white blood cells (shown in blood tests).

Rare (may affect up to 1 in 1 000 people)
- back pain, joint pain
- feeling hot, reddening of the face or other areas of the skin (feeling flushed)
- itchy skin rash
- feeling drowsy
- sleep problems
- ring in the ear
- vomiting
- low blood pressure
- chest pain (not related to the heart)
- numbness, blurred vision
- sudden nervous breakdown, change in mood
- infection and inflammation in the bladder (cystitis)
- haemorrhoids
- conjunctivitis (a type of eye inflammation)
- low level of potassium (shown in blood tests)
- modifications (or disturbances) in heart rhythm
- heart valve disorder (mitral valve incompetence)
- coating of the tongue, difficulty swallowing, dry mouth, belching, abnormal taste after medicine intake
- decreased blood flow to the heart muscle (myocardial ischemia)
- high levels of creatine phosphokinase//creatine phosphokinase MB - which indicates sudden decreased blood flow to the heart muscle (shown in blood tests)
- high levels of troponin - which indicates heart muscle dysfunction (shown in blood tests)
- high levels of the pigment bilirubin - which indicates liver dysfunction (shown in blood tests)
- high levels of myoglobin – which indicates muscle injury (shown in blood tests)
- high levels of blood urea – which indicates kidney dysfunction (shown in blood tests)
- high level of 'lymphocytes'– type of white blood cell which help the body fight disease (shown in blood tests)
- low level of white blood cells (shown in blood tests)
- ECG (electrocardiogram) problems (called 'ST segment depression', 'ST-T segment abnormal' 'bundle branch block right/left', and 'atrioventricular block second degree')

Reporting of side effects
If you get any side effects, talk to your doctor, 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 Akynzeo

- 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 vial after 'EXP'. The expiry date refers to the last day of that month.
- Store below 25°C.
- Keep the vial in the outer carton in order to protect from light.
- The total time from dilution to the start of the infusion should not exceed 24 hours. Store the diluted solution below 25°C.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Akynzeo contains
- The active substances are fosnetupitant and palonosetron. Each vial contains 235 mg of fosnetupitant and 0.25 milligrams of palonosetron.
- The other ingredients are mannitol, disodium edetate (E386), sodium hydroxide (E524), hydrochloric acid diluted (E507) (for pH adjustment) and water.

This medicine contains sodium, see section 2 for more information.

What Akynzeo looks like and contents of the pack
Akynzeo concentrate for solution for infusion is a sterile, clear, colourless to slightly yellow solution and is supplied in a pack of one single-dose 20 mL Type I glass vial with rubber stopper and aluminium cap. Each vial contains one dose.

Pack of 1 vial.

Marketing Authorisation Holder and Manufacturer:

Helsinn Birex Pharmaceuticals Ltd.
Damastown
Mulhuddart
Dublin 15
Ireland

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

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This leaflet was last revised in

Other sources of information

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

The following information is intended for medical or healthcare professionals only:

Instructions of how to dilute AKYNZEO 235 mg/0.25 mg

Preparation of Akynzeo

Step 1	Aseptically prepare an infusion vial or bag filled with 30 mL of 5% glucose injection, or sodium chloride 9 mg/ml (0.9%) solution for injection.
Step 2	Aseptically withdraw the entire volume of concentrate from the AKYNZEO vial and transfer it into the infusion vial or bag containing 30 mL of 5% glucose injection or sodium chloride 9 mg/ml (0.9%) solution for injection to yield a total volume of 50 mL.
Step 3	Before administration, inspect the final diluted solution for particulate matter and discolouration. Discard the vial or bag if particulates and/or discolouration are observed.

The diluted final solution is stable for 24 hours at 25°C.

Parenteral medicines should be inspected visually for particulate matter and discoloration before administration whenever solution and container permit.

The appearance of the diluted solution is the same as the appearance of the diluent.

Discard any remaining solution and waste material. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

The medicinal product must not be diluted or mixed with solutions for which physical and chemical compatibility has not been established (see Summary of Product Characteristic (SmPC), section 6.2).

Package Leaflet: Information for the patient

Akynzeo 300 mg/0.5 mg oral suspension in sachet
netupitant/palonosetron

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

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

What is in this leaflet

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

1. What Akynzeo is and what it is used for

What Akynzeo is
Akynzeo contains two-active substances called:
- netupitant
- palonosetron.

What Akynzeo is used for
Akynzeo is used to help prevent adults with cancer feeling sick (nausea) or being sick (vomiting) while having cancer treatment called 'chemotherapy'.

How Akynzeo works
Chemotherapy medicines can cause the body to release substances called serotonin and substance P. This stimulates the vomiting centre in the brain, making you feel or be sick. The medicines in Akynzeo attach to the receptors in the nervous system through which serotonin and substance P work: netupitant (an NK_1 receptor antagonist) blocks the receptors for substance P, and palonosetron (a 5-HT_3 receptor antagonist) blocks certain receptors for serotonin. By blocking the actions of substance P and serotonin in this way, the medicines help prevent the stimulation of the vomiting centre and the resulting sickness.

2. What you need to know before you take Akynzeo

Do not take Akynzeo if
- you are allergic to netupitant or palonosetron, or any of the other ingredients of this medicine (listed in section 6). If you are not sure, talk to your doctor, pharmacist or nurse before taking this medicine.
- you are pregnant.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before taking Akynzeo if:

- you have liver problems
- you have a blockage in your gut, or you have had constipation in the past
- you or one of your close relatives has ever had a heart problem called 'QT interval prolongation'
- you have any other heart problems
- you have been told you have an imbalance of minerals in your blood such as potassium and magnesium that has not been corrected.

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

Children and adolescents
Akynzeo should not be taken by children and adolescents under 18 years.

Other medicines and Akynzeo
Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines.

In particular tell your doctor, pharmacist or nurse if you are taking any of the following medicines:
- medicines for depression or anxiety called SSRIs (selective serotonin re-uptake inhibitors) - such as fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram or escitalopram
- medicines for depression or anxiety called SNRIs (serotonin noradrenaline re-uptake inhibitors) - such as venlafaxine or duloxetine.

Also tell your doctor, pharmacist or nurse if you are taking any of the following medicines as your doctor may need to change the dose of these other medicines:
- medicines that might cause abnormal heartbeat such as amiodarone, nicardipine, quinidine, moxifloxacin, haloperidol, chlorpromazine, quetiapine, thioridazine or domperidone
- medicines with a narrow therapeutic range that are primarily metabolised by CYP3A4, such as cyclosporine, tacrolimus, sirolimus, everolimus, alfentanil, diergotamine, ergotamine, fentanyl, or quinidine
- some chemotherapy medicines - such as docetaxel or etoposide
- erythromycin - to treat bacterial infections
- midazolam - a sedative used to treat anxiety
- dexamethasone - can be used to treat feeling and being sick
- ketoconazole - to treat Cushing's syndrome
- rifampicin - to treat tuberculosis (TB) and other infections.

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

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Do not take Akynzeo if you are pregnant or if you are a woman of childbearing potential not using contraception.

Do not breast-feed if you are taking Akynzeo. This is because it is not known whether the medicine passes into breast milk.

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

Akynzeo contains sorbitol (E420), sodium and potassium
Sorbitol is a source of fructose. If your doctor has told you that you (or your child) have an intolerance to some sugars or if you have been diagnosed with hereditary fructose intolerance (HFI), a rare genetic disorder in which a person cannot break down fructose, talk to your doctor before you (or your child) take or receive this medicine.

This medicine contains 32.2 mg sodium (main component of cooking/table salt) in each sachet. This is equivalent to 1.61% of the recommended maximum daily dietary intake of sodium for an adult.

This medicine contains 2.60 mg potassium per sachet. To be taken into consideration by patients with reduced kidney function or patients on a controlled potassium diet.

3. How to take Akynzeo

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

How much to take
- The recommended dose is one sachet (each sachet contains 300 mg of netupitant and 0.5 mg of palonosetron).
- Take the sachet about 1 hour before you start your chemotherapy cycle.
- You can take Akynzeo with or without food.
- Squeeze the entire contents of the sachet directly into the mouth.

Akynzeo is taken before the chemotherapy to prevent sickness and feelings of sickness from developing. Do not take Akynzeo in the days after you have chemotherapy - unless you are about to have another chemotherapy cycle.

If you take more Akynzeo than you should
The usual dose is 1 sachet. If you think you may have taken more than you should, tell your doctor straight away. The symptoms of overdose may include headache, dizziness, constipation, anxiety, palpitations, euphoric mood and pain in the legs.

If you forget to take Akynzeo
If you think you have forgotten to take your dose, tell your doctor straight away.

If you stop taking Akynzeo
Akynzeo is taken to help prevent you feeling and being sick when you are having chemotherapy. If you do not want to take Akynzeo, discuss this with your doctor. If you decide not to take Akynzeo (or another similar medicine), your chemotherapy is likely to make you feel sick and be sick.

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

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects
Stop taking Akynzeo and tell your doctor straight away if you notice the following serious side effect - you may need urgent medical treatment:

Very rare: (may affect up to 1 in 10 000 people)
- severe allergic reaction signs include hives, skin rash, itching, difficulty breathing or swallowing, swollen mouth, face, lips, tongue or throat and sometimes a drop in blood pressure.

Other side effects
Tell your doctor, pharmacist or nurse if you notice any of the following side effects:

Common: (may affect up to 1 in 10 people)
- headache
- constipation
- feeling tired.

Uncommon: (may affect up to 1 in 100 people)
- hair loss
- lack of energy (feeling weak)
- decreased appetite
- high blood pressure
- raised, itchy rash on the skin (hives)
- problems with the muscles in your heart (cardiomyopathy)
- spinning sensation (vertigo), feeling dizzy or trouble sleeping (insomnia)
- stomach problems including stomach discomfort, feeling bloated, nausea, pain, indigestion, hiccups, wind or diarrhoea
- high levels of certain enzymes, including blood alkaline phosphatase and liver transaminases (shown in blood tests)
- high levels of creatinine - which measures kidney function (shown in blood tests)
- ECG (electrocardiogram) problems (called 'QT and PR interval prolongation', 'conduction disorder', 'tachycardia' and 'atrioventricular block first degree')
- low levels of 'neutrophils' - a kind of white blood cell which fight infections (shown in blood tests)
- high level of white blood cells (shown in blood tests).

Rare: (may affect up to 1 in 1 000 people)
- back pain, joint pain
- feeling hot, reddening of the face or other areas of the skin (feeling flushed)
- itchy skin rash
- feeling drowsy
- sleep problems
- ring in the ear
- vomiting
- low blood pressure
- chest pain (not related to the heart)
- numbness, blurred vision
- sudden nervous breakdown, change in mood
- infection and inflammation in the bladder (cystitis)
- haemorrhoids
- conjunctivitis (a type of eye inflammation)
- low level of potassium (shown in blood tests)
- modifications (or disturbances) in heart rhythm
- heart valve disorder (mitral valve incompetence)
- coating of the tongue, difficulty swallowing, dry mouth, belching, abnormal taste after medicine intake
- decreased blood flow to the heart muscle (myocardial ischemia)
- high levels of creatine phosphokinase/ creatine phosphokinase MB - which indicates sudden decreased blood flow to the heart muscle (shown in blood tests)
- high levels of troponin - which indicates heart muscle dysfunction (shown in blood tests)
- high levels of the pigment bilirubin - which indicates liver dysfunction (shown in blood tests)
- high levels of myoglobin – which indicates muscle injury (shown in blood tests)
- high levels of blood urea – which indicates kidney dysfunction (shown in blood tests)

- high level of 'lymphocytes'– type of white blood cell which help the body fight disease (shown in blood tests)
- low level of white blood cells (shown in blood tests)
- ECG (electrocardiogram) problems (called 'ST segment depression', 'ST-T segment abnormal' 'bundle branch block right/left', and 'atrioventricular block second degree')

Reporting of side effects
If you get any side effects, talk to your doctor, 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 Akynzeo

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 sachet after 'EXP'. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Akynzeo contains
- The active substances are palonosetron and netupitant. Each sachet contains 300 mg of netupitant and palonosetron hydrochloride equivalent to 0.5 mg of palonosetron.
- The other ingredients are glycerol (E422), xanthan gum, citric acid, sodium citrate dihydrate, potassium sorbate and sorbitol liquid (non-crystallising) (E420).

This medicine contains sodium, potassium and sorbitol (E420), see section 2 for more information.

What Akynzeo looks like and contents of the pack
White to off-white homogeneous suspension.
Pack size containing 1 or 4 PET/ALU/PE (polyester /aluminium/polyethylene) sachet(s) in a single outer carton.
Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Helsinn Birex Pharmaceuticals Ltd.
Damastown
Mulhuddart
Dublin 15
Ireland

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

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