1. NAME OF THE MEDICINAL PRODUCT

Akynzeo 300 mg/0.50 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipients with known effect:

Each capsule contains 7 mg of sorbitol 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 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 for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy.

4.2 Posology and method of administration

Posology

Adults
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 dosage 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
Dosage 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 dosage 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 in each hard capsule.
The additive effect of concomitantly administered medicinal products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account.
The content of sorbitol 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 µg ethinylestradiol and 300 µg 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 metabolized 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 metabolized 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 metabolized 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 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 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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il/

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 tumor. 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
No data available.

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 metabolized. 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% metabolized 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 ($t_{½}$) of palonosetron was 37 ± 12 hours (mean ± SD), and in cancer patients, $t_{½}$ 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 dosage 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 dosage 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 tumors, endocrine neoplasms (in thyroid, pituitary, pancreas, adrenal medulla) and skin tumors 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
Sucrose lauric acid esters
Povidone K-30
Croscarmellose sodium
Purified water
Silicon dioxide/ silica colloidal hydrated
Sodium stearyl fumarate
Magnesium stearate (vegetable grade)

Palonosetron soft capsule
Capsule content:
Glycerol monocaprylocaproate (Type I)
Glycerin (anhydrous)
Purified water
Polyglyceryl oleate
Butylated hydroxyanisole (E320)

Geltain Capsule shell
Gelatin (type 195)
Sorbitol(A810,50/50 w/Glycerin)
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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

Alu/alu blister containing hard capsule(s).
Pack size of one capsule or four capsules.
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. MANUFACTURER:
Helsinn Birex Pharmaceuticals Ltd., Dublin, Ireland.

8. REGISTRATION HOLDER: Rafa Laboratories Ltd., P.O.Box 405, Jerusalem 9100301.
Registration number: 155 79 34343

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