1. NAME OF THE MEDICINAL PRODUCT

Akynzeo 235 mg/0.25 mg

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 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 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 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 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-HT3 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 C YP3 A4 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 µg ethinyl estradiol 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 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 $5\text{-}HT_3$ 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 0.91-1.31]. 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. 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.

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_1receptor 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.

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 (Tmax) 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 Ml 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 M1and 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 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 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 body weight 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
Sodium hydroxide (for pH adjustment)
Hydrochloric acid (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

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

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 REGISTRATION HOLDER

Rafa Laboratories Ltd., P.O. Box 405, Jerusalem 9100301, Israel.

Registration number: 176-41-37355

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