Akynzeo

1. NAME OF THE MEDICINAL PRODUCT

AKYNZEO® 300 mg / 0.5 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient(s) with known effect:

Each capsule contains 7 mg of sorbitol and 20 mg of sucrose. 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 caramelcap with "HE1" printed on the body. The hard capsule is filled with three intermediate netupitant tablets and one intermediate palonosetron softgel.

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 anddelayednausea andvomitingassociatedwith moderately emetogenic cancer 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 AKYNZEO® (see section 4.5 and clinical studies administration schedule in section 5.1).

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

Paediatric population
The safety and efficacy of AKYNZEO® in the paediatric population have not been established. No da ta are available.

Renal impairment
Dosage adjustment is not considered necessary in patients with mild to severe renal impairment. Rena l excretion for netupitant is negligible. Mild to moderate renal impairment does not significantly affect palonosetron pharmacokinetic parameters. Totalsystemic 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 AKYNZEO® 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, AKYNZEO® should be used with caution in these patients (see sections 4.4 and 5.2).

Method of administration

For oral use.
The hard capsule should be swallowed whole. 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. Cases of constipation with faecal impaction requiring hospitalisation have been reported in association with palonosetron 0.75 mg.

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 medicinalproducts (including selective serotonin reuptake inhibitors (SSRIs) and serotonin noradrenaline reuptake inhibitors (SNRIs). Appropriate observation of patients for serotonin syndrome-like symptoms is advised.

QT Prolongation

An ECG study was conducted in adult male andfemale healthy volunteers with oralnetupitanteither 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: thelargest point estimate of the placebo and baseline corrected QTc intervalwas 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 placeboand baseline corrected QTcI was constantly within 10 ms at all time points over 2 days after study drugadministration.

However, since AKYNZEO® contains a 5-HT_3 receptor antagonist, caution should be exercised in concomitant use with medicinalproducts 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 f a m ily 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 andhypomagnesaemia

should be corrected prior to administration.

This product should not be used to prevent nausea and vomiting in the days followingchemotherapy 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 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, such as cyclosporine, tacrolimus, sirolimus, everolimus, alfentanil, diergotamine, ergotamine, fentanyl, and quinidine (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 irinoteca n. Furthermore, netupitant may also affect the efficacy of chemotherapeutic agents that need activation by CYP3A4 metabolism.

Excipients

AKYNZEO® contains sorbitoland sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicinal product.
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.

4.5 Interaction with other medicinal products and other forms of interaction

When AKYNZEO® is used concomitantly with another CYP3A4 inhibitor, netupitant plasma concentrations could be elevated. When AKYNZEO® is used concomitantly with medicinalproducts that induce CYP3A4 activity, netupitant plasma concentrations could be reduced and this may result in decreased efficacy. This product can increase plasma concentrations of concomitantly administered medicinal products that are metabolized 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 bothrenalexcretion andmetabolic 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 havebeenobserved between oralnetupitant andoral 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 oraldexamethasone dose should be reduced by approximately 50% when co-administered with AKYNZEO® (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 AKYNZEO®. No consistent effect was seen with cyclophosphamide after netupitant coadministration.

Oral contraceptives
AKYNZEO®, 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 hormonalcontraception 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 potentialeffects of increased plasma concentrations of midazolam or other benzodiazepines metabolized via CYP3A4 (alprazolam, triazolam) should be considered when coadministering these active substances with AKYNZEO®.

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 and SNRIs) (see section 4.4).

Effect of other medicinal products on the pharmacokinetics of AKYNZEO®

Netupitant is mainly metabolized by CYP3A4; therefore, co-administration with medicinalproducts 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 concomitantadministration with strong CYP3A4 inducers (e.g., rifampicin) should be avoided.

Effect of ketoconazole and rifampicin

Administration of the CYP3A4 inhibitor ketoconazole with AKYNZEO® increased the AUC of netupitant 1.8 fold and C_{max} 1.3 fold when compared to the administration of AKYNZEO® alone. Co-administation 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 CYP3 A4 inhibitors (e.g., ketoconazole) should be approached with caution andconcomitant administration with strong CYP3A4 inducers (e.g. rifampicin) should be avoided.

Additional interactions

AKYNZEO® is unlikely to interact with medicinalproducts 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 AKYNZEO®. A pregnancy test should be performed on allpre-menopausalwomen prior to treatment. Women of childbearing potentialmust use effective contraception duringtherapy 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 ind icate direct or indirect harmful effects of palonosetron with the respect to reproductive toxicity (see section 5.3).

AKYNZEO® is contraindicated duringpregnancy.

Breast-feeding

It is unknown whether palonosetron or netupitant are excreted in human milk. A risk to the suckling child cannot be excluded. AKYNZEO® should not be used duringbreast-feeding. Breast-feedingshould be discontinued duringtreatment with AKYNZEO®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

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

The safety profile of AKYNZEO® was evaluated in 1169 cancer patients receiving at least one cycle of highly emetogenic or moderately emetogenic cancer chemotherapies in three double blind, active - controlled studies, Adverse reactions reported at a greater incidence with AKYNZEO® than with ora l palonosetron 0.5 mg alone, 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).

Adverse reactions per system organ class

System organ class	Common adverse Reactions	Uncommon adverse reactions	Rare adverse reactions
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
Eye disorders			Conjunctivitis
			Vision blurred
Ear and labyrinth disorders		Vertigo	
Cardiac disorders		Atrioventricular block first degree	Arrhythmia
		Cardiomyopathy	Atrioventricular block second degree
		Conduction disorder	Bundle branch block
			Mitral valve incompetence
			Myocardial ischaemia
			Ventricular extrasystoles
Vascular disorders		Hypertension	Hypotension
Respiratory, thoracic and mediastinal disorders		Hiccups	
Gastrointestinal disorders	Constipation	Abdominal pain	Dysphagia
		Diarrhoea	Tongue coated
		Dyspepsia	
		Flatulence	
		Nausea	
Skin and subcutaneous tissue disorders		Alopecia	
		Urticaria	
Musculoskeletal and connective tissue disorders			Back pain
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 MB increased
		Blood creatinine increased	Electrocardiogram ST segment depression
		Electrocardiogram QT prolonged	Electrocardiogram ST-T segment abnormal
			Troponin increased

Description of selected adverse reactions

No common adverse reactions are attributable to netupitant, the new component of the fixed combination, since their frequency was similar with oral palonosetron alone. In addition eye swelling, dyspnoea and myalgia as adverse rea ctions have been reported with oralpalonosetron but not observed during the development of AKYNZEO®. All these reactions were uncommon.

Very rare cases of anaphylaxis, anaphylactic/anaphylactoid reactions and shock have been reported from the post-marketing use of intravenouspalonosetron.

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.

4.9 Overdose

No specific information is available on the treatment of overdose with AKYNZEO®. Netupitant doses up to 600 mg and palonosetron doses up to 6 mg have been used in clinical studies without any safety concerns. In case of overdose, the product should be discontinued and general supportive trea tm ent and monitoring should be provided. Because of the antiemetic activity of netupitant and palonosetron, emesis induced by a medicinalproductmay not be effective. Dialysis studies have not beenperformed. 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 strongbinding 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 vagalafferents 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 centralandperipheralnervous 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 ca ncer 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 oraldose 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.

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 below.

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

	AKYNZEO®	Palonosetron 0.5 mg	
	N=135	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	98.5	93.4	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.

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 studymedication. 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 endpointwas 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.

Proportionof patientsreceiving anthracyclineandcyclophosphamidechemotherapy responding by treatment group and phase – cycle1

	AKYNZEO®	Palonosetron 0.5 mg	
	N=724	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 extensionfor up to 7 additionalcycles of chemotherapy. Antiemetic activity of AKYNZEO® was maintained throughoutrepeat 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 receivingeither Highly Emetogenic Chemotherapy or Moderately Emetogenic Chemotherapy

In a separate study, a total of 413 patients undergoing initial and repeat cycles of chemothera py (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 oralstudies, netupitant was measurable in plasma between 15 minutes and 3 hours a f ter 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 f old increa se 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 oraladministration, palonosetron is wellabsorbed 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 oraldose of palonosetron 0.5 mg one hour prior to chemotherapy, C_{max} was 0.93 ± 0.34 ng/m L a nd T_{max} was 5.1 ± 5.9 hours. The AUC was 30% higher in cancer patients than in healthy subjects. A high fat mealdid not affect the C_{max} and AUC of oralpalonosetron.

Distribution

Netupitant
After a single oral 300 mg dose administration in cancer patients, netupitant disposition was characterised by a two compartment modelwith an estimated median systemic clearance of 20.5 L/h and a large distribution volume in the centralcompartment (486 L). Humanplasma protein binding of netupitant and its two major metabolites M1 and M3 is > 99% at concentrations ranging f rom 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 beendetected in human plasma at netupitantoraldoses of 30 mg andhigher (the desmethylderivative, 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 decreasinggradually beyond 24 h post-dose, indicating that netupitant is beingrapidly 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* m eta bolism studies have suggested that CYP2D6 and to a lesser extent, CYP3A4 and CYP1A2 are involved in the metabolism of palonosetron. However, clinicalpharmacokinetic parameters are notsignificantly 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-exponentialfashion, with an apparentmean elimination half-life of 88 hours in cancer

patients.
Renalclearance is not a significant elimination route for netupitant-relatedentities. The mean fraction of an oraldose 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 f rom 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 andtotalexposure 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 m ild to moderate hepatic impairment. Limited data exist in patients with severe hepatic impairment (Child Pugh score ≥9).

Palonosetron
Hepatic impairmentdoes not significantly affect totalbody clearance of palonosetron compared to the healthy subjects. While the terminalelimination half-life and meansystemic 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. I n the ADME trial, less than 5% of allnetupitant-related materialwas 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 andmarkers of renaldysfunction.

Palonosetron
Mild to moderate renal impairment does not significantly affect palonosetron PK parameters. Tota l 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 beenevaluated in patients with end-stage renal disease.

5.3 Preclinical safety data

Palonosetron
Effects in non-clinicalstudies 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. Animalstudies do not indicate direct or indirect harmfuleffects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. Only lim ited 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, adrenalmedulla) andskin 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 safetypharmacology andsingle and repeated dose toxicity were observed only at exposures considered in excess of the maximum humanexposure, indicating little relevance to clinica l 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 fin dings 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 a nim a ls 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 relevanceof these findings in humans is unknown. No data from animal studies with netupitant are a vaila ble 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 capsule
Capsule content
Glycerol monocaprylocaproate (type I)
Glycerol
Polyglyceryl oleate
Purified water
Butylhydroxyanisole (E320)

Capsule shell
Gelatin
Glycerol
Sorbitol
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

3 years.

6.4 Special precautions for storage

Do not store above 30°C

6.5 Nature and contents of container

Aluminum blister containing one hard capsule.
Box of 1 blister of 1 hard capsule.

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

Manufactured by Helsinn Birex Pharmaceuticals Ltd
Dublin 15, Ireland
Registered and Imported by PT. Pyridam Farma Tbk, Jakarta - Indonesia
Appointed by Juniper Biologics Pte., Ltd., 1 Wallich Street, #30-01A, Guoco Tower, Singapore 078881
Under license :
Helsinn Healthcare SA
Lugano - Switzerland

8. MARKETING AUTHORISATION NUMBER(S)

Registration Number DKI1751900401A1

HARUS DENGAN RESEP DOKTER

SPC February 2022

Informasi Produk untuk Pasien

Akynzeo®

Netupitant/Palonosetron
300mg/0.5mg

Baca semua leaflet ini dengan seksama sebelum Anda mulai menggunakan obat ini karena mengandung informasi penting untuk Anda.

- Simpan leaflet ini. Anda mungkin perlu membacanya kembali.
- Jika Anda memiliki pertanyaan lebih lanjut, tanyakan kepada dokter, apoteker atau perawat.
- Obat ini telah diresepkan hanya untuk Anda. Jangan memberikannya kepada orang lain. Hal tersebut dapat membahayakan mereka, bahkan jika mereka memiliki tanda-tanda penyakit yang sama seperti Anda.
- Jika Anda mengalami efek samping, informasikan kepada dokter Anda, apoteker atau perawat. Termasuk semua efek samping yang mungkin terjadi yang tidak tercantum dalam leaflet ini. Lihat bagian 4.

Apa yang ada dalam leaflet ini

1. Apakah Akynzeo dan apa kegunaannya

Apakah Akynzeo

Akynzeo berisi dua zat berkasiat yaitu :
• netupitant
• palonosetron.

Apa kegunaan Akynzeo

Akynzeo digunakan untuk membantu orang dewasa yang mengidap penyakit kanker mencegah rasa mual atau muntah selama menjalani pengobatan kanker yang disebut 'kemoterapi'.

Bagaimana Akynzeo bekerja

Obat-obat kemoterapi dapat menyebabkan tubuh melepaskan zat yang disebut serotonin dan substansi P. Hal ini merangsang pusat muntah di otak, membuat Anda merasa mual atau muntah. Zat berkhasiat yang terkandung dalam Akynzeo akan menempel pada reseptor di sistem saraf dimana tempat serotonin dan substansi P akan be kerja: netupitant (suatu antagonis reseptor NK1) akan menghambat reseptor substansi P, dan palonosetron (suatu

antagonis reseptor 5- HT3) menghambat reseptor-reseptor tertentu untuk serotonin. Dengan menghalangi kerja substansi P dan serotonin dengan cara ini, obat ini membantu mencegah stimulasi yang menyebabkan rasa mual dan muntah.

2. Apa yang perlu Anda ketahui sebelum Anda menggunakan Akynzeo

Jangan menggunakan Akynzeo bila :

- Anda alergi terhadap netupitant dan palonosetron, atau salah satu bahan lain yang terkandung dalam obat ini (tercantum di bagian 6). Jika Anda tidak yakin, tanyakan kepada dokter Anda, apoteker atau perawat sebelum menggunakan obat ini.
- Anda sedang hamil.

Peringatan dan perhatian :

Informasikan kepada dokter Anda, apoteker atau perawat sebelum menggunakan Akynzeo bila :

- Anda memiliki gangguan hati atau ginjal
- Anda mengalami penyumbatan di usus Anda atau Anda pernah mengalami sembelit sebelumnya
- Anda atau salah satu kerabat dekat Anda pernah memiliki gangguan jantung yang disebut ' perpanjangan interval QT '
- Anda memiliki gangguan jantung lainnya
- Anda pernah diberitahu bahwa Anda mengidap ketidakseimbangan mineral dalam darah seperti kalium dan magnesium yang belum disembuhkan.

Jika salah satu hal di atas terjadi pada Anda (atau Anda tidak yakin), bicarakan dengan dokter Anda, apoteker atau perawat sebelum menggunakan Akynzeo.

Anak-anak dan remaja

Akynzeo tidak boleh digunakan oleh anak-anak dan remaja di bawah 18 tahun.

Obat-obatan lain dan Akynzeo

Beritahu dokter Anda, apoteker atau perawat jika Anda menggunakan, baru-baru ini menggunakan atau akan menggunakan obat-obatan lainnya.

Secara khusus beritahukan dokter Anda, apoteker atau perawat jika Anda sedang menggunakan obat-obatan berikut:

- obat-obat untuk depresi atau kegelisahan yang disebut SSRI (selective serotonin re-uptake inhibitor) - seperti fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram atau escitalopram
- obat untuk depresi atau kecemasan yang disebut SNRIs (serotonin noradrenalin re-uptake inhibitor) - seperti venlafaxine atau duloxetine.

Jika salah satu hal di atas terjadi pada Anda (atau Anda tidak yakin), bicarakan dengan dokter Anda, apoteker atau perawat sebelum menggunakan Akynzeo.

Juga beritahukan dokter Anda, apoteker atau perawat jika Anda sedang menggunakan obat-obatan berikut karena dokter Anda mungkin perlu mengubah dosis obat-obat tersebut :

- obat-obatan yang mungkin menyebabkan detak jantung tidak normal seperti amiodarone, nicardipine, quinidine, moksifloksasin, haloperidol, chlorpromazine, quetiapine, thioridazine atau domperidone
- beberapa obat kemoterapi - seperti docetaxel atau etoposid
- eritromisin - untuk mengobati infeksi bakteri
- midazolam - obat penenang yang digunakan untuk mengobati kegelisahan
- deksametason – yang digunakan untuk mengatasi mual dan muntah
- ketoconazole - untuk mengobati sindrom Cushing
- rifampisin - untuk mengobati tuberkulosis (TB) dan infeksi lainnya.

Jika salah satu hal di atas terjadi pada Anda (atau Anda tidak yakin), bicarakan dengan dokter Anda, apoteker atau perawat sebelum mengambil Akynzeo.

Kehamilan dan menyusui

Bila Anda sedang hamil atau menyusui, kemungkinan hamil atau berencana untuk memiliki bayi, tanyakan kepada dokter Anda untuk mendapatkan saran sebelum menggunakan obat ini.

Jangan menggunakan Akynzeo jika Anda sedang hamil atau jika Anda adalah seorang wanita dengan usia subur yang tidak menggunakan kontrasepsi.

Jangan menyusui bila Anda menggunakan Akynzeo. Hal ini dikarenakan tidak diketahui apakah obat dapat keluar melalui ASI.

Mengemudi dan menggunakan mesin

Anda dapat merasa pusing atau lelah setelah menggunakan Akynzeo. Jika ini terjadi, jangan mengemudi atau menggunakan alat atau mesin.

Akynzeo mengandung sukrosa, sorbitol dan mungkin mengandung sisa kedelai. Obat ini mengandung sukrosa dan sorbitol (jenis gula). Jika Anda telah diberitahukan oleh dokter Anda bahwa Anda memiliki intoleransi untuk beberapa gula, hubungi dokter Anda sebelum menggunakan obat ini.
Ini mungkin mengandung sisa lesitin - yang berasal dari kedelai. Jika Anda alergi terhadap kacang atau kedelai, segera temui dokter Anda bila Anda mengalami tanda-tanda reaksi alergi. Tanda-tanda tersebut termasuk bercak-bercak, ruam kulit, gatal-gatal, kesulitan bernapas atau menelan, bengkak pada mulut, wajah, bibir, lidah atau tenggorokan dan kadang-kadang penurunan tekanan darah.

3. Bagaimana menggunakan Akynzeo

Selalu minum obat ini sesuai dengan yang dokter Anda informasikan kepada Anda. Tanyakan kepada dokter Anda, apoteker atau perawat jika Anda tidak yakin.

Berapa banyak untuk digunakan

- Dosis yang dianjurkan adalah satu kapsul keras (masing-masing kapsul keras mengandung 300 mg netupitant dan 0,5 mg palonosetron).
- Gunakan kapsul keras sekitar 1 jam sebelum Anda memulai siklus kemoterapi Anda.
- Anda dapat menggunakan Akynzeo dengan atau tanpa makanan.

Akynzeo digunakan sebelum kemoterapi untuk mencegah timbulnya mual dan muntah. Jangan menggunakan Akynzeo pada hari-hari setelah Anda menjalani kemoterapi - kecuali jika Anda akan menjalankan siklus kemoterapi lain.

Jika Anda menggunakan Akynzeo lebih dari yang seharusnya

Dosis yang biasa adalah 1 kapsul keras. Jika Anda berpikir mungkin Anda telah menggunakan lebih dari yang seharusnya, segera beritahukan dokter Anda.

Jika Anda lupa untuk menggunakanl Akynzeo

Jika Anda berpikir Anda lupa untuk menggunakan dosis Anda, segera beritahukan dokter Anda.

Jika Anda berhenti menggunakan Akynzeo

Akynzeo digunakan untuk membantu Anda mencegah mual dan muntah ketika Anda menjalani kemoterapi. Jika Anda tidak ingin menggunakan Akynzeo, bicarakan hal ini dengan dokter Anda. Jika Anda memutuskan untuk tidak menggunakan Akynzeo (atau obat lain yang serupa), kemoterapi Anda mungkin membuat Anda mual dan muntah.

Jika Anda memiliki pertanyaan lebih lanjut mengenai penggunaan obat ini, tanyakan kepada dokter Anda, apoteker atau perawat.

4. Kemungkinan efek samping

Seperti semua obat-obatan, obat ini dapat menyebabkan efek samping, meskipun tidak semua orang mengalaminya.

Efek samping yang serius

Hentikan penggunaan Akynzeo dan segera beritahukan dokter Anda jika Anda melihat efek samping yang serius berikut - Anda mungkin perlu perawatan medis segera :

Sangat jarang: dapat terjadi 1 dalam 10.000 orang

- reaksi alergi yang parah - tanda-tanda termasuk bercak-bercak, ruam kulit, gatal-gatal, kesulitan bernapas atau menelan, bengkak pada mulut, wajah, bibir, lidah atau tenggorokan dan kadang-kadang penurunan tekanan darah.

Efek samping lain

Beritahu dokter Anda, apoteker atau perawat jika Anda mengalami salah satu dari efek samping berikut:

Umum: dapat dapat terjadi pada 1 dari 10 orang

- sakit kepala
- sembelit
- merasa lelah.

Jarang : dapat terjadi pada 1 dalam 100 orang

- rambut rontok
- merasa lemah
- nafsu makan menurun
- tekanan darah tinggi
- peningkatan, gatal-gatal ruam pada kulit (bercak-bercak)
- gangguan pada otot-otot jantung (cardiomyopathy)
- sensasi berputar (vertigo), merasa pusing atau kesulitan tidur (insomnia)
- masalah perut termasuk rasa tidak nyaman pada perut, mual, nyeri, gangguan pencernaan, cegukan, kembung atau diare
- tingginya kadar enzim tertentu, termasuk enzim dalam darah dan hati (ditunjukkan dalam tes darah)
- tingginya kadar kreatinin - yang mengukur fungsi ginjal (ditunjukkan dalam tes darah)
- EKG (electrokardiogram) bermasalah (disebut ' perpanjangan Interval QT dan PR ' dan 'gangguan konduksi')
- rendahnya tingkat 'neutrofil' - semacam sel darah putih yang melawan infeksi (terlihat dalam tes darah)
- tingkat tinggi sel darah putih (terlihat dalam tes darah).

Sangat jarang: dapat mempengaruhi hingga 1 dari 1.000 orang

- sakit punggung
- merasa panas
- masalah tidur
- tekanan darah rendah
- Nyeri dada (tidak berhubungan dengan jantung)
- mati rasa, penglihatan kabur
- tiba-tiba merasa gugup, perubahan suasana hati

- infeksi dan peradangan kandung kemih (sistitis)
- konjungtivitis (sejenis radang mata)
- Kadar kalium rendah (terlihat dalam tes darah)
- modifikasi (atau gangguan) irama jantung
- gangguan katup jantung (mitral valve inkompetensi)
- Terlihat lapisan diatas lidah, kesulitan menelan, rasa yang tidak normal setelah menelan obat
- penurunan aliran darah ke otot jantung (iskemia miokard)
- tingginya kadar creatin fosfokinase MB - yang menunjukkan penurunan tiba-tiba aliran darah ke otot jantung (terlihat dalam tes darah)
- tingginya kadar troponin - yang menunjukkan disfungsi otot jantung (terlihat dalam tes darah)
- tingginya kadar pigmen bilirubin - yang menunjukkan disfungsi hati (terlihat dalam tes darah)
- tingginya 'jenis lymphocytes'- sel darah putih yang membantu tubuh melawan penyakit (terlihat dalam tes darah)
- rendahnya sel darah putih (terlihat dalam tes darah)

Pelaporan efek samping

Jika Anda mengalami efek samping, bicarakan dengan dokter Anda, apoteker atau perawat. Hal ini termasuk semua efek samping yang terjadi yang tidak tercantum dalam leaflet ini. Anda juga dapat melaporkan efek samping langsung melalui sistem pelaporan nasion al . Dengan melaporkan efek samping, Anda dapat membantu memberikan informasi lebih lanjut tentang keamanan obat ini.

5. Bagaimana cara menyimpan Akynzeo

- Jauhkan obat ini dari pandangan dan jangkauan anak-anak.
- Jangan menggunakan obat ini setelah kadaluwarsa sesuai yang tertera pada karton dan blister setelah tulisan 'EXP'. Tanggal kadaluwarsa mengacu pada hari terakhir dari bulan tersebut.
- Obat ini tidak memerlukan kondisi penyimpanan khusus.
- Jangan membuang obat-obatan melalui saluran air limbah atau sampah rumah tangga. Tanyakan apoteker Anda bagaimana cara untuk membuang obat-obatan yang tidak lagi digunakan. Langkah-langkah ini akan membantu melindungi lingkungan.

6. Kemasan dan informasi lainnya

Apa yang terkadung dalam Akynzeo

- Zat berkhasiat : palonosetron dan netupitant. Setiap kapsul keras mengandung tiga tablet (300 mg netupitant), dan satu kapsul lunak (palonosetron hidroklorida setara dengan 0,5 miligram palonosetron).

Bahan-bahan lainnya adalah selulosa mikrokristalin (E460), sukrosa ester asam laurat, povidone K-30, kroskarmelosa natrium, koloid silika terhidrasi, natrium stearil fumarat,

magnesium stearat, gliserol monocaprylocaproate (tipe I), gliserol, polyglyceryl oleat, air murni, butilhidroksianisola (E320), gelatin, sorbitol, 1,4 sorbitan, titanium dioksida (E171), lak glaze (diesterifikasi sebagian), oksida besi kuning, merah dan hitam (E172), propilen glikol (E1520).

Obat ini mengandung sukrosa, sorbitol dan mungkin sisa kedelai - lihat bagian 2 untuk informasi lebih lanjut.

Seperti apa Akynzeo terlihat dan apa isi kemasannya

Kapsul keras *opaque* dengan bagian badan berwarna putih dan tutup karamel dengan 'HE1' tercetak pada badan kapsul. Kemasan yang berisi 1 kapsul dalam blister aluminium.

Diproduksi oleh:
Helsinn Birex Pharmaceuticals Ltd.
Dublin 15, Ireland

Didaftarkan dan diimpor oleh:
PT. PYRIDAM FARMA Tbk
Jakarta – Indonesia

Ditunjuk oleh:
Juniper Biologics Pte., Ltd.
1 Wallich Street, #30-01A, Guoco Tower, Singapore 078881

Atas lisensi dari:
Helsinn Healthcare SA
Lugano - Switzerland

Nomor izin edar : DKI1751900401A1

HARUS DENGAN RESEP DOKTER

PYRIDAM FARMA JAKARTA - INDONESIA

Juniper Biologics

SPC February 2022