

**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

## 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 caramel cap with “HE1” printed on the body. The hard capsule is filled with three tablets and one soft capsule.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Akynzeo is indicated in adults for the:

- Prevention of acute and delayed nausea and vomiting associated with highly emetogenic cisplatin-based cancer chemotherapy.
- Prevention of acute and delayed nausea and vomiting associated with moderately emetogenic cancer chemotherapy.

### 4.2 Posology and method of administration

#### Posology

##### *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 data are available.

### *Renal impairment*

Dosage adjustment is not considered necessary in patients with mild to severe renal impairment. Renal excretion for netupitant is negligible. Mild to moderate renal impairment does not significantly affect palonosetron pharmacokinetic parameters. Total systemic exposure to intravenous palonosetron increased by approximately 28% in severe renal impairment relative to healthy subjects. The pharmacokinetics of palonosetron or netupitant has not been studied in subjects with end-stage renal disease requiring hemodialysis and no data on the effectiveness or safety of 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  $\geq 9$ ). 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<sub>3</sub> 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.

#### QT Prolongation

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

1.5 mg palonosetron). Upper 95% confidence limit of the point estimates of placebo and baseline corrected QTcI was constantly within 10 ms at all time points over 2 days after study drug administration.

However, since Akynzeo contains a 5-HT<sub>3</sub> 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 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 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 irinotecan. Furthermore, netupitant may also affect the efficacy of chemotherapeutic agents that need activation by CYP3A4 metabolism.

#### Excipients

Akynzeo contains sorbitol and 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 medicinal products 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 both renal excretion and metabolic pathways, with the latter mediated via multiple CYP enzymes. Palonosetron is mainly metabolised by CYP2D6, with minor contribution by CYP3A4 and CYP1A2 isoenzymes. Based on *in vitro* studies, palonosetron does not inhibit or induce cytochrome P450 isoenzyme at clinically relevant concentrations.

### Interaction between oral netupitant and oral palonosetron:

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

### Interaction with CYP3A4 substrates:

#### *Dexamethasone*

Co-administration of a single dose of 300 mg netupitant with a dexamethasone regimen (20 mg on Day 1, followed by 8 mg twice daily from Day 2 to Day 4) significantly increased the exposure to dexamethasone in a time and dose dependent manner. The  $AUC_{0-24}$  (Day 1), the  $AUC_{24-36}$  (Day 2) and the  $AUC_{84-108}$  and  $AUC_{84-\infty}$  (Day 4) of dexamethasone increased 2.4-fold, with co-administration of 300 mg netupitant. The pharmacokinetic profile of netupitant was unchanged when administered in combination with dexamethasone.

As such, the oral dexamethasone dose should be reduced by approximately 50% when co-administered with 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 co-administration.

#### *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 hormonal contraception are unlikely. No relevant changes of netupitant and palonosetron pharmacokinetics were observed.

#### *Erythromycin and Midazolam*

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

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

There have been reports of serotonin syndrome following concomitant use of 5-HT<sub>3</sub> 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 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.

#### 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-administration with ketoconazole did not affect the pharmacokinetics of palonosetron.

Administration of the CYP3A4 inducer rifampicin with Akynzeo alone decreased the AUC of netupitant 5.2 fold and  $C_{max}$  2.6 fold. Co-administration of rifampicin did not affect the

pharmacokinetics of palonosetron. Consequently, concomitant administration with strong CYP3A4 inhibitors (e.g., ketoconazole) should be approached with caution and concomitant administration with strong CYP3A4 inducers (e.g. rifampicin) should be avoided.

#### Additional interactions

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

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

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

In vitro data show that netupitant is a P-gp inhibitor. In a study performed in healthy volunteers, netupitant does not affect the exposure of digoxin, a P-gp substrate, whereas it increases its C<sub>max</sub> 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 all pre-menopausal women prior to treatment.

Women of childbearing potential must use effective contraception during therapy and up to one month after treatment with this medicinal product.

##### Pregnancy

###### *Netupitant*

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

###### *Palonosetron*

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

Akynzeo is contraindicated during pregnancy.

##### 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 during breast-feeding. Breast-feeding should be discontinued during treatment 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 oral 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 ( $\geq 1/10$ )

Common ( $\geq 1/100$  to  $< 1/10$ )

Uncommon ( $\geq 1/1,000$  to  $< 1/100$ )

Rare ( $\geq 1/10,000$  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
<i>Infections and infestations</i>			Cystitis
<i>Blood and lymphatic system disorders</i>		Neutropenia	Leukopenia
		Leucocytosis	Lymphocytosis
<i>Metabolism and nutrition disorders</i>		Decreased appetite	Hypokalaemia
<i>Psychiatric disorders</i>		Insomnia	Acute psychosis
			Mood altered
			Sleep disorder
<i>Nervous system disorders</i>	Headache	Dizziness	Hypoaesthesia
<i>Eye disorders</i>			Conjunctivitis
			Vision blurred
<i>Ear and labyrinth disorders</i>		Vertigo	
<i>Cardiac disorders</i>		Atrioventricular block first degree	Arrhythmia
		Cardiomyopathy	Atrioventricular block second degree
		Conduction disorder	Bundle branch block
			Mitral valve incompetence
			Myocardial ischaemia
			Ventricular extrasystoles
<i>Vascular disorders</i>		Hypertension	Hypotension
<i>Respiratory, thoracic and mediastinal disorders</i>		Hiccups	
<i>Gastrointestinal disorders</i>	Constipation	Abdominal pain	Dysphagia
		Diarrhoea	Tongue coated
		Dyspepsia	
		Flatulence	
		Nausea	
<i>Skin and subcutaneous tissue disorders</i>		Alopecia	
		Urticaria	
<i>Musculoskeletal and connective tissue disorders</i>			Back pain
<i>General disorders and administration site conditions</i>	Fatigue	Asthenia	Feeling hot
			Non-cardiac chest pain
			Product taste abnormal
<i>Investigations</i>		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 reactions have been reported with oral palonosetron 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 intravenous palonosetron.

### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

## **4.9 Overdose**

No 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 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<sub>3</sub>) antagonists; ATC code: A04AA55

#### Mechanism of action

Netupitant is a selective antagonist of human substance P/neurokinin 1 (NK<sub>1</sub>) receptors.

Palonosetron is a 5-HT<sub>3</sub> 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<sub>3</sub> receptors located on vagal afferents to initiate the vomiting reflex.

Delayed emesis has been associated with the activation of tachykinin family neurokinin 1 (NK<sub>1</sub>) 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<sub>1</sub> receptor occupancy of 92.5%, 86.5%, 85.0%, 78.0%, and 76.0% in striatum at 6, 24, 48, 72, and 96 hours, respectively, after administration of 300 mg netupitant.

#### Clinical efficacy and safety

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

### Highly Emetogenic Chemotherapy (HEC) study

In a multicenter, randomized, parallel, double-blind, controlled clinical study of 694 patients, the efficacy and safety of single doses of oral netupitant in combination with oral palonosetron was compared with a single oral dose of palonosetron in cancer patients receiving a chemotherapy regimen that included cisplatin (median dose = 75 mg/m<sup>2</sup>). 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 N=135 %	Palonosetron 0.5 mg N=136 %	p-value
Primary endpoint			
Complete response Overall phase <sup>§</sup>	89.6	76.5	0.004
Major secondary endpoints			
Complete response Acute phase <sup>‡</sup>	98.5	89.7	0.007
Delayed phase <sup>†</sup>	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

<sup>‡</sup>Acute phase: 0 to 24 hours post-cisplatin treatment.

<sup>†</sup>Delayed phase: 25 to 120 hours post-cisplatin treatment.

<sup>§</sup>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**

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

After completion of cycle 1, patients had the option to participate in a multiple-cycle extension, receiving the same treatment as assigned in cycle 1. There was no pre-specified limit of the number of repeat consecutive cycles for any patient. A total of 1450 patients (Akynzeo n=725; Palonosetron n=725) received study medication. Of these, 1438 patients (98.8%) completed cycle 1 and 1286 patients (88.4%) continued treatment in the multiple-cycle extension. A total of 907 patients (62.3%) completed the multiple-cycle extension up to a maximum of eight treatment cycles. A total of 724 patients (99.9%) were treated with cyclophosphamide. All patients were additionally treated with either doxorubicin (68.0%) or epirubicin (32.0%).

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

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

**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 <sup>†</sup>	76.9	69.5	0.001
Major secondary endpoints			
Complete response Acute phase <sup>‡</sup> Overall phase <sup>§</sup>	88.4 74.3	85.0 66.6	0.047 0.001
No emesis Acute phase Delayed phase Overall phase	90.9 81.8 79.8	87.3 75.6 72.1	0.025 0.004 <0.001
No significant nausea Acute phase Delayed phase Overall phase	87.3 76.9 74.6	87.9 71.3 69.1	N.S. 0.014 0.020

\* p-value from Cochran-Mantel-Haenszel test, stratified by age class and region.

<sup>‡</sup> Acute phase: 0 to 24 hours after anthracycline and cyclophosphamide regimen

<sup>†</sup> Delayed phase: 25 to 120 hours after anthracycline and cyclophosphamide regimen

<sup>§</sup> Overall: 0 to 120 hours after anthracycline and cyclophosphamide regimen

Patients continued into the Multiple-Cycle extension for up to 7 additional cycles of chemotherapy. Antiemetic activity of Akynzeo was maintained throughout repeat cycles for those patients continuing in each of the multiple cycles.

The impact of nausea and vomiting on patients' daily lives was assessed using the Functional Living Index–Emesis (FLIE). The proportion of patients with Overall no impact on daily life was 6.3% higher (p value =0.005) in the Akynzeo group (78.5%) than in the palonosetron group (72.1%).

*Multiple-cycle safety study in patients receiving either Highly Emetogenic Chemotherapy or Moderately Emetogenic Chemotherapy*

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

Paediatric population

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

## 5.2 Pharmacokinetic properties

### Absorption

#### *Netupitant*

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

In 82 healthy subjects given a single oral dose of netupitant 300 mg, maximum plasma netupitant concentration ( $C_{max}$ ) was  $486 \pm 268$  ng/mL (mean  $\pm$  SD) and median time to maximum concentration ( $T_{max}$ ) was 5.25 hours, the AUC was  $15032 \pm 6858$  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<sub>0-∞</sub> and  $C_{max}$  increased by 1.1 fold and 1.2 fold, respectively, after a high fat meal.

#### *Palonosetron*

Following oral administration, palonosetron is well absorbed with its absolute bioavailability reaching 97%. After single oral doses using buffered solution mean maximum palonosetron concentrations ( $C_{max}$ ) and area under the concentration-time curve (AUC<sub>0-∞</sub>) 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  $0.81 \pm 1.66$  ng/mL (mean  $\pm$  SD) and time to maximum concentration ( $T_{max}$ ) was  $5.1 \pm 1.7$  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  $0.93 \pm 0.34$  ng/mL and  $T_{max}$  was  $5.1 \pm 5.9$  hours. The AUC was 30% higher in cancer patients than in healthy subjects. A high fat meal did not affect the  $C_{max}$  and AUC of oral palonosetron.

### Distribution

#### *Netupitant*

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

#### *Palonosetron*

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

### Biotransformation

#### *Netupitant*

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

M2 and M3 metabolites were all shown to be pharmacologically active in an animal pharmacodynamic model, where M3 was most potent and M2 least active.

#### *Palonosetron*

Palonosetron is eliminated by multiple routes with approximately 50% metabolized to form two primary metabolites: N-oxide-palonosetron and 6-S-hydroxy-palonosetron. These metabolites each have less than 1% of the 5-HT<sub>3</sub> receptor antagonist activity of palonosetron. *In vitro* metabolism studies have suggested that CYP2D6 and to a lesser extent, CYP3A4 and CYP1A2 are involved in the metabolism of palonosetron. However, clinical pharmacokinetic parameters are not significantly different between poor and extensive metabolizers of CYP2D6 substrates.

#### Elimination

##### *Netupitant*

Following administration of a single dose of Akynzeo, netupitant is eliminated from the body in a multi-exponential fashion, with an apparent mean elimination half-life of 88 hours in cancer patients. Renal clearance is not a significant elimination route for netupitant-related entities. The mean fraction of an oral dose of netupitant excreted unchanged in urine is less than 1%; a total of 3.95% and 70.7% of the radioactive dose was recovered in the urine and faeces, respectively.

Approximately half the radioactivity administered orally as [14C]-netupitant was recovered from urine and faeces within 120 h of dosing. Elimination via both routes was estimated to be complete by Day 29-30 post-dose.

##### *Palonosetron*

Following administration of a single oral 0.75 mg dose of [14C]-palonosetron to six healthy subjects, 85% to 93% of the total radioactivity was excreted in urine, and 5% to 8% was eliminated in faeces. The amount of unchanged palonosetron excreted in the urine represented approximately 40% of the administered dose. In healthy subjects given palonosetron capsules 0.5 mg, the terminal elimination half-life ( $t_{1/2}$ ) of palonosetron was  $37 \pm 12$  hours (mean  $\pm$  SD), and in cancer patients,  $t_{1/2}$  was  $48 \pm 19$  hours. After a single dose of approximately 0.75 mg intravenous palonosetron, the total body clearance of palonosetron in healthy subjects was  $160 \pm 35$  mL/h/kg (mean  $\pm$  SD) and renal clearance was  $66.5 \pm 18.2$  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  $\geq 9$ ).

##### *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<sub>CR</sub>) 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 sternbrae and agenesis of accessory lung lobe were observed following daily administration of netupitant in rabbits at 10 mg/kg/day and higher during the period of organogenesis. In a pilot dose range finding study in rabbits, cleft palate, microphtalmia and aphakia were observed in four foetuses from one litter in the 30 mg/kg/day group. The relevance of these findings in humans is unknown. No data from animal studies with netupitant are available regarding placental transfer and lactation. Netupitant is not mutagenic.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

#### Hard capsule content:

##### *Netupitant tablets*

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

##### *Palonosetron soft 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**

4 years.

### **6.4 Special precautions for storage**

This medicinal product does not require any special storage conditions.

### **6.5 Nature and contents of container**

Alu/alu blister containing one or two hard capsules.

Pack size of one capsule or perforated unit dose pack of 4x1 capsules.

#### **6.6 Special precautions for disposal**

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

#### **7. MARKETING AUTHORISATION HOLDER**

Helsinn Birex Pharmaceuticals Ltd.  
Damastown  
Mulhuddart  
Dublin 15  
Ireland.

#### **8. MARKETING AUTHORISATION NUMBER(S)**

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

#### **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 27 May 2015

#### **10. DATE OF REVISION OF THE TEXT**

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

## **ANNEX II**

- A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

**A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**

Name and address of the manufacturer(s) responsible for batch release

Helsinn Birex Pharmaceuticals Ltd.  
Damastown,  
Mulhuddart  
Dublin 15  
Ireland

**B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

Medicinal product subject to medical prescription.

**C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

• **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

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

• **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

**ANNEX III**  
**LABELLING AND PACKAGE LEAFLET**

## **A. LABELLING**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON**

**1. NAME OF THE MEDICINAL PRODUCT**

Akynzeo 300 mg / 0.5 mg hard capsules  
Netupitant / Palonosetron

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

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

**3. LIST OF EXCIPIENTS**

Also contains sucrose and sorbitol. See package leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

1 hard capsule  
4x1 hard capsules (unit dose)

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
Oral use.

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

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

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

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

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

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/15/1001/001 1 hard capsule  
EU/1/15/1001/002 4x1 hard capsules (unit dose)

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

akynzeo

**17. UNIQUE IDENTIFIER – 2D BARCODE**

<2D barcode carrying the unique identifier included.>

**18. UNIQUE IDENTIFIER – HUMAN READABLE DATA**

PC:  
SN:  
NN:

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTER**

**1. NAME OF THE MEDICINAL PRODUCT**

Akynzeo 300 mg / 0.5 mg hard capsules  
Netupitant / Palonosetron

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

Helsinn

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. OTHER**

**B. PACKAGE LEAFLET**

## Package Leaflet: Information for the patient

### Akynzeo 300 mg / 0.5 mg hard capsules Netupitant / Palonosetron

- ▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

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

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

#### What is in this leaflet

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

#### 1. What Akynzeo is and what it is used for

##### What Akynzeo is

Akynzeo contains two medicines ('active substances') called:

- netupitant
- palonosetron.

##### What Akynzeo is used for

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

##### How Akynzeo works

Chemotherapy medicines can cause the body to release substances called serotonin and substance P. This stimulates the vomiting centre in the brain, making you feel or be sick. The medicines in Akynzeo attach to the receptors in the nervous system through which serotonin and substance P work: netupitant (an NK<sub>1</sub> receptor antagonist) blocks the receptors for substance P, and palonosetron (a 5-HT<sub>3</sub> receptor antagonist) blocks certain receptors for serotonin. By blocking the actions of substance P and serotonin in this way, the medicines help prevent the stimulation of the vomiting centre and the resulting sickness.

#### 2. What you need to know before you take Akynzeo

##### Do not take Akynzeo if:

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

- you are pregnant.

### **Warnings and precautions**

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

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

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

### **Children and adolescents**

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

### **Other medicines and Akynzeo**

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

In particular tell your doctor, pharmacist or nurse if you are taking any of the following medicines:

- medicines for depression or anxiety called SSRIs (selective serotonin re-uptake inhibitors) - such as fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram or escitalopram
- medicines for depression or anxiety called SNRIs (serotonin noradrenaline re-uptake inhibitors) - such as venlafaxine or duloxetine.

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

Also tell your doctor, pharmacist or nurse if you are taking any of the following medicines as your doctor may need to change the dose of these other medicines:

- medicines that might cause abnormal heartbeat such as amiodarone, nicardipine, quinidine, moxifloxacin, haloperidol, chlorpromazine, quetiapine, thioridazine or domperidone
- some chemotherapy medicines - such as docetaxel or etoposide
- erythromycin - to treat bacterial infections
- midazolam - a sedative used to treat anxiety
- dexamethasone - can be used to treat feeling and being sick
- ketoconazole - to treat Cushing's syndrome
- rifampicin - to treat tuberculosis (TB) and other infections.

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

### **Pregnancy and breast-feeding**

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

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

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

### **Driving and using machines**

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

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

It may contain traces of lecithin - which comes from soya. If you are allergic to peanut or soya, see your doctor straight away if you notice any signs of an allergic reaction. The signs may include hives, skin rash, itching, difficulty breathing or swallowing, swollen mouth, face, lips, tongue or throat and sometimes a drop in blood pressure.

### **3. How to take Akynzeo**

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

#### **How much to take**

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

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

#### **If you take more Akynzeo than you should**

The usual dose is 1 capsule. If you think you may have taken more than you should, tell your doctor straight away.

#### **If you forget to take Akynzeo**

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

#### **If you stop taking Akynzeo**

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

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

### **4. Possible side effects**

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

#### **Serious side effects**

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

**Very rare:** may affect up to 1 in 10,000 people

- severe allergic reaction – signs include hives, skin rash, itching, difficulty breathing or swallowing, swollen mouth, face, lips, tongue or throat and sometimes a drop in blood pressure.

**Other side effects**

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

**Common:** may affect up to 1 in 10 people

- headache
- constipation
- feeling tired.

**Uncommon:** may affect up to 1 in 100 people

- hair loss
- feeling weak
- decreased appetite
- high blood pressure
- raised, itchy rash on the skin (hives)
- problems with the muscles in your heart (cardiomyopathy)
- spinning sensation (vertigo), feeling dizzy or trouble sleeping (insomnia)
- stomach problems including stomach discomfort, nausea, pain, indigestion, hiccups, wind or diarrhoea
- high levels of certain enzymes, including blood and liver enzymes (shown in blood tests)
- high levels of creatinine - which measures kidney function (shown in blood tests)
- ECG (electrocardiogram) problems (called ‘QT and PR interval prolongation’ and ‘conduction disorder’)
- low levels of ‘neutrophils’ - a kind of white blood cell which fight infections (shown in blood tests)
- high level of white blood cells (shown in blood tests).

**Rare:** may affect up to 1 in 1,000 people

- back pain
- feeling hot
- sleep problems
- low blood pressure
- chest pain (not related to the heart)
- numbness, blurred vision
- sudden nervous breakdown, change in mood
- infection and inflammation in the bladder (cystitis)
- conjunctivitis (a type of eye inflammation)
- low level of potassium (shown in blood tests)
- modifications (or disturbances) in heart rhythm
- heart valve disorder (mitral valve incompetence)
- coating of the tongue, difficulty swallowing, abnormal taste after medicine intake
- decreased blood flow to the heart muscle (myocardial ischemia)
- high levels of creatin phosphokinase MB - which indicates sudden decreased blood flow to the heart muscle (shown in blood tests)
- high levels of troponin - which indicates heart muscle dysfunction (shown in blood tests)
- high levels of the pigment bilirubin - which indicates liver dysfunction (shown in blood tests)
- high level of ‘lymphocytes’ – type of white blood cell which help the body fight disease (shown in blood tests)
- low level of white blood cells (shown in blood tests)

## Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the [national reporting system](#) listed in [Appendix V](#). By reporting side effects, you can help provide more information on the safety of this medicine.

## 5. How to store Akynzeo

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

## 6. Contents of the pack and other information

### What Akynzeo contains

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

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

### What Akynzeo looks like and contents of the pack

The hard capsules are opaque with a white body and a caramel cap with 'HE1' printed on the body. Pack size containing 1 capsule in an aluminium blister or (perforated) unit dose pack containing 4 capsules (2 capsules per aluminium blister strip).

### Marketing Authorisation Holder and Manufacturer:

Helsinn Birex Pharmaceuticals Ltd.  
Damastown  
Mulhuddart  
Dublin 15  
Ireland

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

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**This leaflet was last revised in**

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