Applicant : Eurolab (Pty) Ltd
Proprietary name : Akynzeo
Dosage form and strength : Capsules 300 mg/0,5 mg (Netupitant & Palonosetron)
Date of submission : 19 September 2022
Approval date : 22 November 2022

APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

AKYNZEO™ 300 mg/0,5 mg capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 300 mg netupitant and palonosetron hydrochloride equivalent to 0,5 mg palonosetron.

Contains sugar (sucrose and sorbitol).

Excipients with known effect

Each capsule contains 20 mg sucrose and 7 mg sorbitol.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Hard capsules

Hard gelatine capsule size 0, caramel-white with “HE1” printed in black on the white part, containing three tablets round, flat, off-white, plain bevelled edge and one softgel plain, round to oval, opaque light beige.

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 section 5.1).

Special populations

Elderly people

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

Renal impairment

Dosage adjustment is not considered necessary in patients with mild to severe renal impairment. Renal excretion for netupitant is negligible. Mild to moderate renal impairment does not significantly affect palonosetron pharmacokinetic parameters. Total systemic exposure to intravenous palonosetron increased by approximately 28 % in severe renal

impairment relative to healthy subjects. The pharmacokinetics of palonosetron or netupitant has not been studied in subjects with end-stage renal disease requiring haemodialysis 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 section 4.4 and section 5.2).

Paediatric population

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

Method of administration

For oral use.

The hard capsule should be swallowed whole and can be taken with or without food.

4.3 Contraindications

- Hypersensitivity to netupitant, palonosetron, or to any of the excipients of AKYNZEO (listed in section 6.1).

- Pregnancy and lactation (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 medicines including selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine (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 supratherapeutic doses (600 mg netupitant and 1,5 mg palonosetron). Upper 95 % confidence limit of the point estimates of placebo and baseline corrected QTcI was constantly within 10 ms at all time points over 2 days after study medicine administration.

However, since AKYNZEO contains a 5-HT_3 receptor antagonist, caution should be exercised in concomitant use with medicines 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, bradydysrhythmia, conduction disturbances and in patients taking antidysrhythmic medicines or other medicines that lead to QT prolongation or electrolyte abnormalities. Hypokalaemia and hypomagnesaemia should be corrected prior to administration.

AKYNZEO should not be used to prevent nausea and vomiting in the days following

chemotherapy if not associated with another chemotherapy administration.

AKYNZEO 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.

AKYNZEO should be used with caution in patients receiving concomitant orally administered medicines that are metabolised primarily through CYP3A4 and with a narrow therapeutic range, such as ciclosporin, tacrolimus, sirolimus, everolimus, alfentanil, diergotamine, ergotamine, fentanyl and quinidine (see section 4.5).

Chemotherapeutic medicines that are substrates for CYP3A4

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

Excipients with known effect

AKYNZEO contains sorbitol and sucrose. Patients with the rare hereditary conditions such as fructose intolerance, glucose-galactose malabsorption, sucrase-isomaltase insufficiency or sorbitol intolerance should not take AKYNZEO.

AKYNZEO may also contain a trace of lecithin derived from soya. Therefore, patients with known hypersensitivity to peanut or soya should be monitored closely for an allergic reaction.

4.5 Interaction with other medicines 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 medicines that induce CYP3A4 activity, netupitant plasma concentrations could be reduced and this may result in decreased efficacy. AKYNZEO can increase plasma concentrations of concomitantly administered medicines that are metabolised via CYP3A4.

In humans, netupitant is eliminated mainly by hepatic metabolism mediated by CYP3A4 with a marginal renal excretion. At a dose of 300 mg in humans, netupitant is a substrate and moderate inhibitor of CYP3A4. Palonosetron is eliminated from the body through both renal excretion and metabolic pathways, with the latter mediated via multiple CYP enzymes. Palonosetron is mainly metabolised by CYP2D6, with minor contribution by CYP3A4 and CYP1A2 isoenzymes. Based on *in vitro* studies, palonosetron does not inhibit or induce cytochrome P450 isoenzyme at clinically relevant concentrations.

Interaction between oral netupitant and oral palonosetron

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

Interaction with CYP3A4 substrates

Dexamethasone

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

2,4-fold, with co-administration of 300 mg netupitant. The pharmacokinetic profile of netupitant was unchanged when administered in combination with dexamethasone. As such, the oral dexamethasone dose should be reduced by approximately 50 % when co-administered with AKYNZEO (see section 4.2).

Chemotherapeutic medicines (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 micrograms ethinylestradiol and 300 micrograms 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. The pharmacokinetic profile of netupitant was unaffected by the concomitant administration of either midazolam or erythromycin. The potential effects of increased plasma concentrations and prolonged half-life of midazolam or other benzodiazepines metabolised via CYP3A4 (alprazolam, triazolam) should be considered when co-administering these medicines with AKYNZEO.

Serotonergic medicines (e.g. SSRIs and SNRIs)

There have been reports of serotonin syndrome following concomitant use of 5-HT_3

antagonists and other serotonergic medicines (including SSRIs and SNRIs) (see section 4.4).

Effect of other medicines on the pharmacokinetics of AKYNZEO

Netupitant is mainly metabolised by CYP3A4; therefore, co-administration with medicines 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 medicines which are P-gp substrates. Netupitant is not a substrate for P-gp. When netupitant was administered on Day 8 of a 12-day regimen of digoxin, no changes in digoxin pharmacokinetics were observed.

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

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

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

In vitro data show that netupitant is a P-gp inhibitor. In a study performed in healthy volunteers, netupitant does not affect the exposure of digoxin, a P-gp substrate, whereas it increases its C_{max} by 1,09-fold (90 % CI 0,9 – 1,31). It is not excluded that this effect may be more marked, and then clinically relevant, in cancer patients, notably those having abnormal renal function. Therefore, caution is recommended when netupitant is combined with digoxin or with other P-gp substrates such as dabigatran, or colchicine.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception in females

Women of childbearing potential should not be pregnant or become pregnant while on treatment with AKYNZEO. A pregnancy test should be performed on all pre-menopausal women prior to treatment. Women of childbearing potential must use highly effective contraception during therapy and for up to one month after treatment with AKYNZEO.

Pregnancy

AKYNZEO is contraindicated during pregnancy (see section 4.3).

Netupitant

Studies in animals have shown reproductive toxicity including teratogenic effects in rabbits without safety margin (see section 5.3).

Palonosetron

Animal data do not indicate direct or indirect harmful effects of palonosetron with respect to reproductive toxicity (see section 5.3).

Breastfeeding

Breastfeeding should be discontinued during treatment with AKYNZEO and for 1 month after the last dose (see section 4.3).

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 an 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

The safety profile of AKYNZEO was evaluated in 1 169 cancer patients receiving at least one cycle of highly emetogenic or moderately emetogenic cancer chemotherapies in three double-blind, active-controlled studies.

Common adverse reactions reported with AKYNZEO were headache (3,6 %), constipation (3,0 %) and fatigue (1,2 %). None of these events was serious.

Tabulated summary of adverse reactions

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 (≥ 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).

MedDRA system organ class	**Frequency**	**Adverse event**
Infections and infestations	Rare	Cystitis
Blood and lymphatic system disorders	Uncommon	Neutropenia, leucocytosis
	Rare	Leukopenia, lymphocytosis
Metabolism and nutrition disorders	Uncommon	Decreased appetite
	Rare	Hypokalaemia
Psychiatric	Uncommon	Insomnia

disorders	Rare	Acute psychosis, altered mood, sleep disorder
Nervous system disorders	Common	Headache
	Uncommon	Dizziness
	Rare	Hypoaesthesia
Eye disorders	Rare	Conjunctivitis, blurred vision
Ear and labyrinth disorders	Uncommon	Vertigo

Cardiac disorders	Uncommon	First degree atrioventricular block, cardiomyopathy, conduction disorder
	Rare	Dysrhythmia, second degree atrioventricular block, bundle branch block, mitral valve incompetence, myocardial ischaemia, ventricular extrasystoles
Vascular disorders	Uncommon	Hypertension
	Rare	Hypotension
Respiratory thoracic and mediastinal disorders	Uncommon	Hiccups
Gastrointestinal disorders	Common	Constipation
	Uncommon	Abdominal pain, diarrhoea, dyspepsia, flatulence, nausea
	Rare	Dysphagia, coated tongue
Skin and subcutaneous tissue disorders	Uncommon	Alopecia, urticaria
Musculoskeletal and connective tissue disorders	Rare	Back pain

General disorders and administration	Common	Fatigue
	Uncommon	Asthenia
	Rare	Feeling hot, non-cardiac chest pain, abnormal product taste
Investigations	Uncommon	Increased liver transaminases, increased blood alkaline phosphatase, increased blood creatinine, prolonged electrocardiogram QT
	Rare	Increased blood bilirubin, increased blood creatine phosphokinase MB, electrocardiogram ST segment depression, abnormal electrocardiogram ST-T segment, increased troponin

Description of selected adverse reactions

No common adverse reactions are attributable to netupitant, 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. 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 medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

No specific information is available on the treatment of overdose with AKYNZEO.

In case of overdose, AKYNZEO should be discontinued and general supportive and symptomatic treatment and monitoring should be provided. Because of the antiemetic activity of netupitant and palonosetron, emesis induced by a medicine may not be effective. Dialysis studies have not been performed. However, due to the large volume of distribution of palonosetron and netupitant, dialysis is unlikely to be an effective treatment for overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

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

Palonosetron is a 5-HT_3 receptor antagonist with a strong binding affinity for this receptor and little or no affinity for other receptors.

Chemotherapeutic medicines produce nausea and vomiting by stimulating the release of serotonin from the enterochromaffin cells of the small intestine. Serotonin then activates 5-HT_3 receptors located on vagal afferents to initiate the vomiting reflex.

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

Netupitant was shown to cross the blood brain barrier with a NK_1 receptor occupancy of 92,5 %, 86,5 %, 85,0 %, 78,0 % and 76,0 % in striatum at 6, 24, 48, 72 and 96 hours, respectively, after administration of 300 mg netupitant.

5.2 Pharmacokinetic properties

Absorption

Netupitant

Absolute netupitant bioavailability data are not available in humans; based on data from two studies with intravenous netupitant, the bioavailability in humans is estimated to be greater than 60 %.

In single dose oral studies, netupitant was measurable in plasma between 15 minutes and 3 hours after dosing. Plasma concentrations followed a first order absorption process and reached C_{max} in approximately 5 hours. There was a supra-proportional increase in C_{max} and AUC parameters for doses from 10 mg to 300 mg.

In 82 healthy subjects given a single oral dose of netupitant 300 mg, maximum plasma netupitant concentration (C_{max}) was 486 ± 268 ng/mL (mean ± SD) and median time to maximum concentration (T_{max}) was 5,25 hours, the AUC was 15 032 ± 6 858 h.ng/mL. In a pooled analysis, females had a higher netupitant exposure compared to males; there was a 1,31-fold increase in C_{max}, a 1,02-fold increase for AUC and a 1,36-fold increase in half-life.

Netupitant $AUC_{0-\infty}$ and C_{max} increased by 1,1-fold and 1,2-fold, respectively, after a high fat meal.

Palonosetron

Following oral administration, palonosetron is well absorbed with its absolute bioavailability reaching 97 %. After single oral doses using buffered solution mean maximum palonosetron concentrations (C_{max}) and area under the concentration-time curve ($AUC_{0-\infty}$) were dose proportional over the dose range of 3,0 to 80 mcg/kg in healthy subjects.

In 36 healthy male and female subjects given a single oral dose of 0,5 mg palonosetron, maximum plasma concentration (C_{max}) was 0,81 ± 1,66 ng/mL (mean ± SD) and time to maximum concentration (T_{max}) was 5,1 ± 1,7 hours. In female subjects (n=18), the mean AUC was 35 % higher and the mean C_{max} was 26 % higher than in male subjects (n=18). In 12 cancer patients given a single oral dose of palonosetron 0,5 mg one hour prior to chemotherapy, C_{max} was 0,93 ± 0,34 ng/mL and T_{max} was 5,1 ± 5,9 hours.The AUC was 30 % higher in cancer patients than in healthy subjects. A high fat meal did not affect the C_{max} and AUC of oral palonosetron.

Distribution

Netupitant

After a single oral 300 mg dose administration in cancer patients, netupitant disposition was characterised by a two-compartment model with an estimated median systemic clearance of 20,5 L/h and a large distribution volume in the central compartment (486 L). Human plasma protein binding of netupitant and its two major metabolites M1 and M3 is > 99 % at concentrations ranging from 10 to 1 500 ng/mL. The third major metabolite, M2, is > 97 % bound to plasma proteins.

Palonosetron

Palonosetron has a volume of distribution of approximately 8,3 ± 2,5 L/kg. Approximately 62

% of palonosetron is bound to plasma proteins.

Biotransformation

Netupitant

Three metabolites have been detected in human plasma at netupitant oral doses of 30 mg and higher (the desmethyl derivative, M1; the N-oxide derivative, M2; the OH-methyl derivative, M3). *In vitro* metabolism studies have suggested that and, to a lesser extent, CYP2D6 and CYP2C9 are involved in the metabolism of netupitant. After administration of a single oral dose of 300 mg netupitant, mean plasma netupitant/plasma radioactivity ratios ranged from 0,13 to 0,49 over 96 h post-dose. The ratios were time dependent with values decreasing gradually beyond 24 h post-dose, indicating that netupitant is being rapidly metabolised. Mean C_{max} was approximately 11 %, 47 % and 16 % of the parent for M1, M2 and M3 respectively; M2 had the lowest AUC relative to the parent (14 %) whereas M1 and M3 AUC were approximately 29 % and 33 % of the parent, respectively. M1, M2 and M3 metabolites were all shown to be pharmacologically active in an animal pharmacodynamic model, where M3 was most potent and M2 least active.

Palonosetron

Palonosetron is eliminated by multiple routes with approximately 50 % metabolised to form two primary metabolites: N-oxide-palonosetron and 6-S-hydroxy-palonosetron. These metabolites each have less than 1 % of the 5-HT_3 receptor antagonist activity of palonosetron. *In vitro* metabolism studies have suggested that CYP2D6 and to a lesser extent, CYP3A4 and CYP1A2 are involved in the metabolism of palonosetron. However, clinical pharmacokinetic parameters are not significantly different between poor and extensive metabolisers of CYP2D6 substrates.

Elimination

Netupitant

Following administration of a single dose of AKYNZEO, netupitant is eliminated from the body in a multi-exponential fashion, with an apparent mean elimination half-life of 88 hours in cancer patients.

Renal clearance is not a significant elimination route for netupitant-related entities. The mean fraction of an oral dose of netupitant excreted unchanged in urine is less than 1 %; a total of 3,95 % and 70,7 % of the radioactive dose was recovered in the urine and faeces, respectively.

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

Palonosetron

Following administration of a single oral 0,75 mg dose of [14C]-palonosetron to six healthy subjects, 85 % to 93 % of the total radioactivity was excreted in urine, and 5 % to 8 % was eliminated in faeces. The amount of unchanged palonosetron excreted in the urine represented approximately 40 % of the administered dose. In healthy subjects given palonosetron capsules 0,5 mg, the terminal elimination half-life (t½) of palonosetron was 37 ± 12 hours (mean± SD), and in cancer patients, t½ was 48 ± 19 hours. After a single dose of approximately 0,75 mg intravenous palonosetron, the total body clearance of palonosetron in healthy subjects was 160 ± 35 mL/h/kg (mean ± SD) and renal clearance was 66,5 ± 18,2 mL/h/kg.

Special populations

Hepatic impairment

Netupitant

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

Palonosetron

Hepatic impairment does not significantly affect total body clearance of palonosetron compared to the healthy subjects. While the terminal elimination half-life and mean systemic exposure of palonosetron is increased in the subjects with severe hepatic impairment, this does not warrant dose reduction.

Renal impairment

Netupitant

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

netupitant and markers of renal dysfunction.

Palonosetron

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

Therefore, AKYNZEO can be administered without dosage adjustment in patients with renal impairment.

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

5.3 Preclinical safety data

Palonosetron

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure, indicating little relevance to clinical use. Non-clinical studies indicate that palonosetron, only at very high concentrations, may block ion channels involved in ventricular de- and re-polarisation and prolong action potential duration. Degeneration of seminiferous epithelium was associated with palonosetron following a one month oral repeat dose toxicity study in rats. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. Only limited data from animal studies are available regarding the placental transfer (see section 4.6). Palonosetron is not mutagenic. High doses of

palonosetron (each dose causing at least 15 times the human therapeutic exposure) applied daily for two years caused an increased rate of liver tumours, endocrine neoplasms (in thyroid, pituitary, pancreas, adrenal medulla) and skin tumours in rats but not in mice. The underlying mechanisms are not fully understood, but because of the high doses employed and since the medicine 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.

Non-clinical studies indicate that netupitant and its metabolites and the combination with palonosetron only at very high concentrations may block ion channels involved in ventricular de- and re-polarisation and prolong action potential duration. Reproductive studies in animals with netupitant do not indicate direct or indirect harmful effects with respect to fertility, parturition or postnatal development. An increased incidence of positional foetal abnormalities of the limbs and paws, fused sternebrae and agenesis of accessory lung lobe were observed following daily administration of netupitant in rabbits at 10 mg/kg/day and higher during the period of organogenesis. In a pilot dose range finding study in rabbits, cleft palate, microphthalmia and aphakia were observed in four foetuses from one litter in the 30 mg/kg/day group. 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

Silica colloidal hydrated

Sodium stearyl fumarate

Magnesium stearate

Palonosetron softgel capsules

Capsule content:

Glycerol monocaprylocaproate

Glycerine (anhydrous)

Polyglyceryl dioleate

Butylated hydroxyanisole (E320)

Capsule shell:

Gelatine

Sorbitol with glycerine blend

Titanium dioxide (E171)

Hard capsule shell

Gelatine

Titanium dioxide (E171)

Yellow iron oxide (E172)

Red iron oxide (E172)

Printing ink

Shellac glaze (partially esterified)

Black iron oxide (E172)

Propylene glycol (E1520)

Ammonium hydroxide (E527)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 25 °C, protected from moisture and light.

Keep the blisters in the carton until required for use.

6.5 Nature and contents of container

Aluminium/aluminium blister containing 1 hard capsule. The blister strip is placed in a carton.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Biomab Innovation (Pty) Ltd.

Woodmead Office Park, 3 Stirrup Lane

Van Reenens Avenue

Woodmead

8. REGISTRATION NUMBER

52/5.7.2/0037

9. DATE OF FIRST AUTHORISATION

24 November 2020

10. DATE OF REVISION OF THE TEXT

November 2022

™ The AKYNZEO trademark is owned by Helsinn Healthcare SA