AKYNZEO®

Name of the Medicine

Netupitant / Palonosetron (as hydrochloride) 300 mg / 500 mcg, Capsule

Netupitant:

Chemical Name:

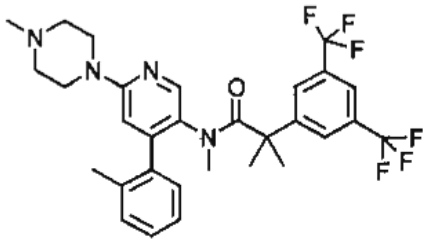
2-[3,5-bis(trifluoromethyl)phenyl]-N,2-dimethyl-N-[4-(2-methylphenyl)-6-(4-methylpiperazin-1-yl)pyridin-3-yl] propanamide

CAS Registry No: 290297-26-6

Molecular Weight: 578.61 g mol^{-1}

Molecular Formula: $C_{30}H_{32}F_6N_4O$

Structural Formula:



PKa_1 : 2.36

PKa_2: 7.65

Partition Coefficient: 5.1

Palonosetron (as hydrochloride):

Chemical Name:

(3aS)-2-[(S)-1-Azabicyclo[2.2.2]oct-3-yl]-2,3,3a,4,5,6-hexahydro-1-oxo-1*H*benz[*de*]isoquinoline hydrochloride.

Palonosetron hydrochloride exists as a single isomer.

CAS Registry No:

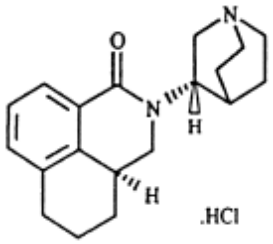
135729-61-2 Palonosetron

135729-62-3 Palonosetron Hydrochloride

Molecular Weight: 332.87.

Molecular Formula: $C_{19}H_{24}N_2O.HCl$

Structural Formula:



PKa_1 : 8.9

Partition Coefficient 4.3 at pH 7.4.

Description

Each AKYNZEO hard gelatin capsule contains three 100 mg netupitant (300 mg total) immediate release tablets and one 500 mcg palonosetron (as hydrochloride) soft capsule.

Each netupitant tablet contains the following excipients: microcrystalline cellulose, sucrose laurate, povidone, croscarmellose sodium, silicon dioxide, sodium stearylfumarate, magnesium stearate.

Each palonosetron soft gel capsule contains the following excipients: Glyceryl caprylate / caprate, glycerol, polyglyceryl -3 dioleate, purified water, butylated hydroxyanisole. The soft capsule shell consists of: gelatin, sorbitol special glycerin blend A-810, glycerol, titanium dioxide (E171).

Each AKYNZEO hard capsule shell consists of gelatin, titanium dioxide, iron oxide yellow and iron oxide red (E172)

Each AKYNZEO hard capsule contains 7 milligrams of sorbitol.

The printing ink contains shellac, iron oxide black (E172), propylene glycol (E1520) and ammonium hydroxide (E527).

Pharmacology

Pharmacotherapeutic group: Antiemetics and antinauseants; serotonin (5-HT_3) and neurokinin-1 (NK_1) receptor antagonists (see mechanism of action).

ATC code: A04AA55 palonosetron, combinations (pending).

Mechanism of action

Netupitant is a selective high-affinity antagonist of human substance P/neurokinin 1 (NK_1) receptors. Palonosetron is a selective serotonin subtype 3 (5-HT_3) receptor antagonist with a strong binding affinity for this receptor. Cancer chemotherapy may be associated with a high incidence of nausea and vomiting, particularly when certain agents, such as cisplatin, are used. 5-HT_3 receptors are located on the nerve terminals of the vagus in the periphery and centrally in the chemoreceptor trigger zone of the area postrema. It is thought that chemotherapeutic agents produce nausea and vomiting by releasing serotonin from the enterochromaffin cells of the small intestine and that the released serotonin then activates 5-HT_3 receptors located on vagal afferents to initiate the vomiting reflex. The development of acute emesis is known to depend on 5-Hydroxytryptamine serotonin (5-HT) and the 5-HT_3 receptor has been demonstrated to selectively participate in the emetic response. Delayed emesis has been largely 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 and palonosetron can contribute to the inhibition of substance P mediated response. *In vitro* studies have demonstrated that while palonosetron does not bind to the NK_1 receptor, it does inhibit cisplatin-induced substance P enhancement of NK_1 signalling, in a dose-dependent manner.

Pharmacodynamic effects

NK_1 Receptor Occupancy

The receptor occupancy for the Chemotherapy Induced Nausea and Vomiting (CINV) dosing regimen of netupitant has been determined in a human Positron Emission Tomography (PET) study with three single doses tested (100 mg, 300 mg and 450 mg, 2 subjects per dose). Netupitant was shown to cross the blood brain barrier with a high occupancy of brain NK_1 receptors. All doses achieved a relatively long duration of blockade of the NK_1 receptor. NK_1 receptor occupancy in striatum at 6, 24, 48, 72 and 96 hours after administration of 300 mg netupitant was 92.5%, 86.5%, 85.0%, 78.0% and 76.0%, respectively.

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 slightly supra-proportional increase in C_{max} and AUC parameters for doses from 10 mg to 300 mg with dose proportional increases between 300 mg and 450 mg.

In healthy subjects given a single oral dose of netupitant 300 mg, maximum plasma netupitant concentration (C_{max}) was 747 ± 200.4 ng/mL (mean ± SD) and time to maximum concentration (T_{max}) was 5.0 hours, the AUC was 25232 ± 6281.7 h.ng/mL. In a pooled analysis, females had a higher netupitant exposure compared to males; there was a 31% increase in C_{max}, a 10% increase for AUC and a 30% increase in half-life. In cancer patients given a single oral dose of netupitant 300 mg one hour prior to chemotherapy (docetaxel, etoposide or cyclophosphamide), C_{max} and AUC of netupitant and its metabolites were similar to that reported in healthy subjects and were independent of the chemotherapeutic regimen administered.

Netupitant $AUC_{0-\infty}$ and C_{max} increased by 16%, and 18%, 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 µg/kg in healthy subjects.

In 36 healthy male and female subjects given a single oral dose of 500 mcg palonosetron, maximum plasma palonosetron 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 500 mcg 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.

<u>Distribution</u>

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 drug concentrations ranging from 10 to 1500 ng/mL. The third major metabolite, M2, is > 97% bound to plasma proteins.

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

Biotransformation

Netupitant
In humans, netupitant is eliminated mainly by hepatic metabolism mediated by CYP3A4. Three major metabolites have been detected in human plasma at netupitant oral doses of 30 mg and higher (M1, the desmethyl derivative, M1; the N-oxide derivative, M2; the OH-methyl derivative, M3). 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 the drug 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.

At a dose of 300 mg in humans, netupitant is a substrate and moderate inhibitor of CYP3A4. Netupitant and its metabolites, M1, M2 and M3, are not inducers of CYP1A2, CYP2C9, CYP2C19 and CYP3A4. When AKYNZEO is used concomitantly with another CYP3A4 inhibitor, netupitant plasma concentrations could be elevated. When AKYNZEO is used concomitantly with medications that induce CYP3A4 activity, netupitant plasma concentrations could be reduced and this may result in decreased efficacy of AKYNZEO. AKYNZEO can increase plasma concentrations of concomitantly administered oral medications that are metabolised via CYP3A4 (see *Interactions with Other Medicines).*

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
Netupitant is eliminated from the body in a multi-exponential fashion, with an apparent mean elimination half-life of 88 hours in cancer patients (after a single oral dose of AKYNZEO).

Renal clearance is not a significant elimination route for the drug-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 [14^C]- 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 [14^C]-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 500 mcg, the terminal elimination half-life ($t_{½}$) of palonosetron was 37 ± 12 hours (mean ± SD), and in cancer patients, $t_{½}$ was 48 ± 19 hours. After a single dose of approximately 0.75 mg intravenous palonosetron, the total body clearance of palonosetron in healthy subjects was 160 ± 35 mL/h/kg (mean ± SD) and renal clearance was 66.5± 18.2 mL/h/kg.

Clinical Studies

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.

<u>Highly Emetogenic Chemotherapy (HEC) study:</u>
In a multicenter, randomised, parallel, double-blind, controlled clinical study of 694 patients (Study 1), the efficacy and safety of single doses of oral netupitant in combination with oral palonosetron, were compared with a single oral dose of palonosetron in cancer patients receiving a chemotherapy regimen that included cisplatin (median dose = 75 mg/m^2). Lung and respiratory tract, head and neck, and ovarian cancers were the most frequent cancer types; approximately half of the enrolled patients had metastatic disease.

The primary efficacy analysis included 135 patients who received a single oral dose of netupitant 300 mg plus palonosetron 500 mcg, and 136 patients who received oral palonosetron 500 mcg alone.

The treatment regimens for the oral netupitant 300 mg plus palonosetron 500 mcg and the palonosetron 500 mcg arms are defined in the following table (Table 1).

Table 1:

Treatment Regimen	Day 1	Days 2 to 4
Netupitant 300 mg plus palonosetron 500 mcg	Netupitant 300 mg PO Palonosetron 500 mcg PO Dexamethasone* 12 mg PO	Dexamethasone* 8 mg PO
Palonosetron	Palonosetron 500 mcg PO Dexamethasone 20 mg PO	Dexamethasone 16 mg PO

*Dexamethasone should be administered 30 minutes prior to chemotherapy treatment on Day 1 and in the morning on Days 2 through 4. The dose of dexamethasone accounts for drug interactions.

Of the 135 patients who received netupitant 300 mg plus palonosetron 500 mcg, 43% were women, and all patients were White. The age ranged from 19 to 77 years, with a mean age of 53 years. During the study 86% of the 135 treated patients in the netupitant 300 mg plus palonosetron 500 mcg arm received a concomitant chemotherapeutic agent in addition to protocol-mandated cisplatin. The most common chemotherapeutic agents and the proportion of patients exposed were cyclophosphamide (34%), fluorouracil (24%), etoposide (21%) and doxorubicin (16%).

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.
Major secondary efficacy endpoints included:

- CR for the 0-24 hour interval (acute phase) and for the 25-120 hour interval (delayed phase);
- Complete protection (defined as no emesis, no rescue therapy, no significant nausea) for the overall, acute and delayed phases.
- No emesis for the overall, acute and delayed phases.
- No significant nausea (maximum VAS <25 mm) and no nausea (maximum VAS <5 mm) for the overall, acute and delayed phases.

A summary of the key results from this study is shown in Table 2.

The proportion of patients with CR in the overall phase was 13.2% (95% CI: 4.4 to 21.9%) higher (p-value = 0.004) in the netupitant 300 mg plus palonosetron 500 mcg group (89.6%) than in the palonosetron group (76.5%). In the acute phase, the proportion of patients with CR was 8.8% higher (p-value=0.007) in the netupitant 300 mg plus palonosetron 500 mcg group

(98.5%) than in the palonosetron group (89.7%). In the delayed phase, the proportion of patients with CR was 10.2% higher (p-value = 0.018) in the netupitant 300 mg plus palonosetron 500 mcg group (90.4%) than in the palonosetron group (80.1%).

Table 2 Proportion of Patients Receiving Cisplatin Chemotherapy Responding by Treatment Group and Phase

	Netupitant 300 mg plus palonosetron 500 mcg N=135 %	Palonosetron 500 mcg PO 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
COMPLETE PROTECTION			
Acute Phase	97.0	87.5	0.006
Delayed Phase	84.4	73.5	0.027
Overall Phase	83.0	69.9	0.010
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
NO NAUSEA			
Acute Phase	80.0	75.0	N.S.
Delayed Phase	68.1	53.7	0.014

Overall Phase	61.5	50.7	N.S.

[‡]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)[1] study

In a multicentre, randomised, 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 500 mcg in cancer patients scheduled to receive the first cycle of an anthracycline and cyclophosphamide regimen for the treatment of a solid malignant tumor. Almost all patients (97%) had breast cancer, which was metastatic in 16% of cases.

At the time of the study, anthracycline-cyclophosphamide containing chemotherapy regimens were considered to be moderately emetogenic. Recent guidelines have updated these regimens to highly emetogenic.

All patients received a single oral dose of dexamethasone.

The treatment regimens for the AKYNZEO and the palonosetron 500 mcg PO arms are displayed in the following table (Table 3).

Table 3:

Treatment Regimen	Day 1	Days 2 to 3
AKYNZEO	Netupitant 300 mg PO Palonosetron 500 mcg PO Dexamethasone* 12 mg PO	No antiemetic treatment
Palonosetron	Palonosetron 500 mcg PO Dexamethasone 20 mg PO	No antiemetic treatment

*Dexamethasone should be administered 30 minutes prior to chemotherapy treatment on Day 1. The dose of dexamethasone accounts for drug interactions.

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) actually 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.

Of the 725 patients who received AKYNZEO study medication, 711 (98%) were women; 79% were White, 14% Asian, 6% Hispanic, and <1% were Black or Other. Age ranged from 22 to 79 years, with a median age of 54 years. 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%).

[1] 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.

During the first cycle, 32% of the 725 patients treated with AKYNZEO received a concomitant chemotherapeutic agent in addition to protocol-mandated regimens, with the most common chemotherapeutic being fluorouracil (28.3%) and docetaxel (2.6%).

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

- CR for the acute and the overall phase;
- Complete protection (defined as no emesis, no rescue therapy, no significant nausea) for the delayed, the acute and the overall phase;
- No emesis for the delayed, the acute and the overall phase;
- No significant nausea (maximum VAS <25 mm) and no nausea (maximum VAS <5 mm) for the delayed, the acute and the overall phase.

A summary of the key results from Study 2 is shown in Table 4.

Table 4 Proportion of Patients Receiving Anthracycline and Cyclophosphamide Chemotherapy Responding by Treatment Group and Phase – Cycle 1

	AKYNZEO N=724 %	Palonosetron 500 mcg PO 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
COMPLETE PROTECTION			
Acute Phase	82.3	81.1	N.S.
Delayed Phase	67.3	60.3	0.005
Overall Phase	63.8	57.9	0.020
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
NO NAUSEA			
Acute Phase	70.4	70.1	N.S.
Delayed Phase	53.3	49.5	N.S.
Overall Phase	50.3	47.2	N.S.

* 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

Complete Response

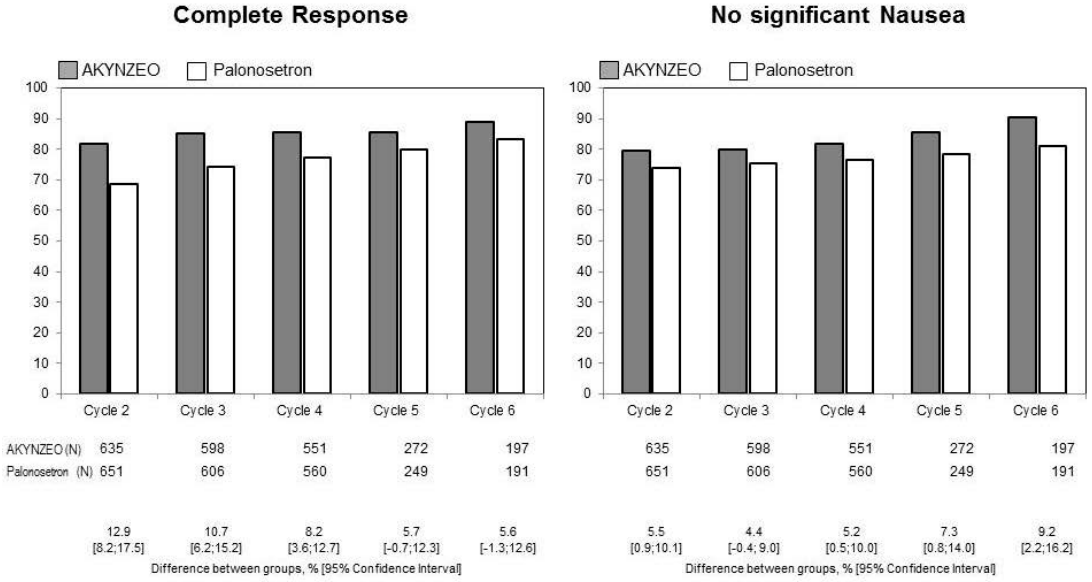
The primary efficacy analysis was conducted in 1449 randomised patients who received the chemotherapy regimen and the study treatment. The proportion of patients with CR in the delayed phase was 7.4% (95% CI: 2.9 to 11.9%) higher (p-value = 0.001) in the AKYNZEO group (76.9%) than in the

palonosetron group (69.5%). In the acute phase, the proportion of patients with CR was 3.4% higher (p-value=0.047) in the AKYNZEO group (88.4%) than in the palonosetron group (85.0%). In the overall phase, the proportion of patients with CR was 7.7% higher (p-value = 0.001) in the AKYNZEO group (74.3%) than in the palonosetron group (66.6%).

Multiple Cycles

Patients continued into the Multiple-Cycle extension for up to 7 additional cycles of chemotherapy. The proportion of patients with complete response and no significant nausea in the delayed phase by treatment group at each cycle (cycles 2 to 6) is displayed in Figure 1. A limited number of patients received treatment beyond cycle 6. During all cycles the CR rate and the proportion of patients with no significant nausea rates in the delayed phase were higher for AKYNZEO than for palonosetron PO. Antiemetic activity of AKYNZEO was maintained throughout repeat cycles for those patients continuing in each of the multiple cycles.

Figure 1 Proportion of Patients Receiving Anthracycline and Cyclophosphamide Chemotherapy with Complete Response and No Significant Nausea by Treatment Group and Cycle in the Delayed Phase



Patient Reported Outcomes

The impact of nausea and vomiting on patients' daily lives was assessed using the Functional Living Index–Emesis (FLIE), a validated specific patient-reported outcome measure of the impact of nausea and vomiting on daily life. The proportion of patients with Overall no impact in daily life was 6.3% higher (p-value =0.005) in the AKYNZEO group (78.5%) than in the palonosetron group (72.1%).

The proportion of patients with no impact in daily life of the Vomiting Domain was 5.6% higher (p-value =0.001) in the AKYNZEO group (90.1%) than in the palonosetron group (84.4%). The proportion of patients with no impact in daily life of the Nausea Domain was 5.8% higher (p-value =0.015) in the AKYNZEO group (71.5%) than in the palonosetron group (65.8%).

Safety study in patients receiving either Highly Emetogenic Chemotherapy or Moderately Emetogenic Chemotherapy

In one multicentre, multinational, randomised, active-controlled, double-blind, double-dummy, unbalanced (3:1), parallel group, clinical study the safety and the efficacy of a single oral dose of AKYNZEO was compared to an antiemetic regimen with aprepitant and palonosetron in cancer patients scheduled to receive either a highly emetogenic chemotherapy or a moderately emetogenic chemotherapy regimen. Patients were randomised (3:1) on Day 1 of their first chemotherapy cycle, before administration of chemotherapy, to the two treatment groups, as displayed in the following table (Table 5), according to the emetogenicity regimen:

Table 5

Treatment Regimen	**Day 1**	**Day 2**	**Day 3**	**Day 4**
HEC patients				
AKYNZEO	Netupitant 300 mg PO Palonosetron 500 mcg PO Dexamethasone 12 mg PO	Dexamethasone 8 mg PO	Dexamethasone 8 mg PO	Dexamethasone 8 mg PO
Aprepitant and Palonosetron	Aprepitant 125 mg PO Palonosetron 500 mcg PO Dexamethasone 12 mg PO	Aprepitant 80 mg PO Dexamethasone 8 mg PO	Aprepitant 80 mg PO Dexamethasone 8 mg PO	Dexamethasone 8 mg PO
MEC patients				
AKYNZEO	Netupitant 300 mg PO Palonosetron 500 mcg PO Dexamethasone 12 mg PO	No Antiemetic Treatment	No Antiemetic Treatment	No Antiemetic Treatment
Aprepitant and Palonosetron	Aprepitant 125 mg PO Palonosetron 500 mcg PO Dexamethasone	Aprepitant 80 mg PO	Aprepitant 80 mg PO	No Antiemetic Treatment

	12 mg PO			

A total of 413 patients were randomised in the study, to receive either AKYNZEO (n=309) or aprepitant and palonosetron (n=104).
Lung and respiratory tract, ovarian, colorectal and head and neck cancer were the most frequent cancer types, with 50% of patients having metastatic disease.

A total of 412 patients received study medication (AKYNZEO n=309; aprepitant and palonosetron n=103), and 23 patients discontinued after randomisation and during any planned chemotherapy cycle. Of the 412 patients who were treated with study medication, 405 patients (98.1%) completed cycle 1 and 376 patients were scheduled for treatment in the following cycles up to a maximum of 14 cycles. A total of 165 patients (40.4%) completed at least 6 cycles of treatment.

Of the 309 patients who were randomised to the AKYNZEO arm and received study medication, 155 (50.2%) were women; 84% were White, 15% Asian, 6% Hispanic, and 1% were Black. The age ranged from 27 to 76 years, with a median age of 57 years.

During the first cycle, a total of 75 patients (24.3%) who were randomised to the AKYNZEO arm and received study medication were treated with a HEC regimen (cisplatin, 96% or dacarbazine, 4%). A total of 234 patients (75.7%) received a MEC regimen, the most common chemotherapeutic agents being carboplatin (60.3%), oxaliplatin (20.1%) and doxorubicin (11.1%).

The primary objective of the study was to assess the safety and tolerability of AKYNZEO in initial and repeated cycles of chemotherapy. The secondary objective of the study was to describe its efficacy.
AKYNZEO safety profile was comparable to aprepitant and palonosetron in patients undergoing initial and repeat cycles of MEC or HEC. Safety data in the AKYNZEO arm have been integrated and described elsewhere (*See Adverse Effects).*

In cycle 1, the proportion of patients with a CR was numerically higher in the AKYNZEO arm compared to aprepitant and palonosetron for the delayed (83.2% vs. 77.7%) and overall (80.6% vs. 75.7%) phases. Efficacy was maintained throughout the study.

No clinically meaningful effect of AKYNZEO on blood pressure, heart rate, and ECG parameters, including QTc, was observed and was comparable to aprepitant and palonosetron in CINV clinical studies.

Paediatric Population
The safety and efficacy of AKYNZEO in children have not been established. No data are available.

Indications

AKYNZEO is indicated in adult patients for:

- *Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy.*
- *Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy.*

Contraindications

Hypersensitivity to palonosetron or netupitant or to any of the excipients listed in *Description.*

Precautions

General

Hypersensitivity reactions to palonosetron may occur in patients who have exhibited hypersensitivity to other selective 5-HT_3 receptor antagonists.

Patients with a history of constipation or signs of subacute intestinal obstruction should be monitored following administration.

A specific thorough ECG study conducted in adult male and female healthy volunteers on netupitant (200 and 600 mg) orally administered with palonosetron (0.5 and 1.5 mg) demonstrated that AKYNZEO had no clinically important effects on ECG parameters. The ECG data analyses including a pharmacodynamic-pharmacokinetic (PD-PK) analysis showed no effects on cardiac repolarisation. However since AKYNZEO contains a $5HT_3$ receptor antagonist caution should be exercised in the concomitant use of AKYNZEO 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, bradyarrhythmias, conduction disturbances and in patients taking anti-arrhythmic agents or other medicinal products that lead to QT prolongation or electrolyte abnormalities. Hypokalemia and hypomagnesemia should be corrected prior to AKYNZEO administration.

AKYNZEO should not be used to prevent or treat nausea and vomiting in the days following chemotherapy if not associated with another chemotherapy administration.

AKYNZEO contains sorbitol. Patients with rare hereditary problems of fructose intolerance, should not take this medicinal product. AKYNZEO capsules 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.

There have been reports of serotonin syndrome with the use of 5-HT_3 antagonists either alone or in combination with other serotonergic drugs including selective serotonin reuptake inhibitors (SSRI) and serotonin noradrenaline reuptake inhibitors (SNRIs).

Concomitant use of CYP3A4 Substrates

Netupitant is a moderate inhibitor of CYP3A4. It has a half-life of 88 hours so its inhibitory effect on CYP3A4 can last for over 4 days. Systemic exposure to chemotherapy agents and other medicines metabolised by CYP3A4 may increase when administered with or after AKYNZEO. For example, exposure to docetaxel was shown to increase by 37% with concomitant use. Likewise, exposure to dexamethasone is clearly increased with concomitant use. Patients should be closely monitored for adverse reactions that may arise from this additional systemic exposure to relevant chemotherapies and other medicines. See '*Interactions with other medicines*' for further details.

Effects on Fertility

Palonosetron at oral doses of up to 60 mg/kg/day (>30 times the human exposure after administration of AKYNZEO based on plasma AUC) was found to have no effect on fertility and reproductive performance of male and female rats. Oral doses of 60 and 120 mg/kg/day given to male rats for 2 months prior to mating associated with complete infertility at the 120 mg/kg/day dose. Testicular degeneration was confirmed in a 3 month general toxicity study at oral doses of 60 and 120 mg/kg/day. An IV dose of up to 10 mg/kg/day (>30 times the human exposure after administration of AKYNZEO based on plasma AUC) had no effect on male fertility and reproductive performance.

Daily oral administration of up to 30 mg/kg netupitant in female (3 times the human AUC at the recommended human dose) and male rats had no effects on fertility or reproductive performance.

Use In Pregnancy (Category B3)

Palonosetron had no effect on foetal development at oral doses of up to 18 mg/kg/day in rats and 90 mg/kg/day in rabbits. At 60 and 120 mg/kg/day in rats, foetal weight was reduced. Palonosetron did not cause foetal abnormalities at these dose levels. However, palonosetron had toxic effects on the dams at 120 mg/kg in rats and 90 mg/kg/day in rabbits.

No effects on embryo-foetal development were observed following daily administration of netupitant in pregnant rats during the period of organogenesis at doses up to 3 times the human AUC at the recommended human dose. However, a dose-dependent increase in adverse effects on embryo-foetal development was observed following daily administration of netupitant in pregnant rabbits during the period of organogenesis with doses at least twice the human AUC at the recommended human dose.

There are no data from the use of palonosetron and netupitant in pregnant women. Animal studies are insufficient with respect to reproductive toxicity of the combination. AKYNZEO should not be used during pregnancy unless the clinical condition of the woman requires treatment with palonosetron and netupitant.

Use In Lactation

It is not known whether palonosetron or netupitant are excreted in human milk. A risk to the newborn/infant cannot be excluded. Breastfeeding should be discontinued during treatment with AKYNZEO. Pre- and post-natal development study in rats with netupitant does not indicate direct or indirect harmful effects on F1 and F2 generations, after daily administration of netupitant up to 3 times the human AUC at the recommended human dose.

Effects on Ability to Drive and Use Machines

No studies on the effects on the ability to drive and use machines have been performed with AKYNZEO. AKYNZEO may induce dizziness, somnolence or fatigue, therefore patients should use caution when driving or operating machines.

Carcinogenicity

In a 104-week carcinogenicity study in CD-1 mice, animals were treated with oral doses of palonosetron at 10, 30 and 60 mg/kg/day. Treatment with palonosetron was not tumorigenic. The highest tested dose produced a systemic exposure to palonosetron (plasma AUC) of > 100 times the human exposure at the recommended oral of 500 mcg in the combination.

In a 104-week palonosetron carcinogenicity study in Sprague-Dawley rats, male and female rats were treated with oral doses of 15, 30 and 60 mg/kg/day and 15, 45 and 90 mg/kg/day, respectively. The lowest and highest doses, respectively, produced a systemic exposure to palonosetron (plasma AUC) of > 4.4 times and > 95.5 times the human exposure at the recommended dose.

Treatment with palonosetron produced increased incidences of adrenal benign pheochromocytoma and combined benign and malignant pheochromocytoma in both male and female rats, of pancreatic Islet cell adenoma and combined adenoma and carcinoma of pancreatic acinar cell adenoma and combined adenoma and adenocarcinoma and of pituitary adenoma in male rats. Increased incidences of skin keratocanthomas and tail squamous cell papillomas were also observed, mainly in males. In female rats, palonosetron produced hepatocellular adenoma and combined hepatocellular adenoma and carcinoma, and increased the incidences of thyroid C-cell adenoma and combined adenoma and carcinoma, and of mammary gland adrenocarcinoma.

No carcinogenicity study was performed with netupitant.

Genotoxicity

Palonosetron was not genotoxic in the Ames test, the Chinese hamster ovarian cell (CHO/HGPRT) forward mutation test, the *ex vivo* hepatocyte unscheduled DNA synthesis test or the mouse micronucleus test. It was, however, positive for clastogenic effects in the CHO cell chromosomal aberration test.

Netupitant did not show mutagenic or clastogenic activity in a standard battery of *in vitro* and *in vivo* genotoxicity tests (Ames, gene mutation in mouse lymphoma cells and rat micronucleus test).

Special Populations:

Geriatrics: Population pharmacokinetic analysis and clinical safety and efficacy data for palonosetron did not reveal any differences between cancer patients ≥ 65 years of age and younger patients (18 to 64 years). In healthy elderly subjects (>65 years old) the mean $AUC_{0-\infty}$ and C_{max} was 25% and 36% higher, respectively, for netupitant, and 37% and 10% higher, respectively, for palonosetron compared to those in healthy younger adults (22-45 years old). No dose adjustment is required for these patients.

Race: Intravenous palonosetron pharmacokinetics was characterised in twenty-four healthy Japanese subjects over the dose range of 3 – 90 µg/kg. Total body clearance was 25% higher in Japanese subjects compared to Whites; however, no dose adjustment is required. The pharmacokinetics of palonosetron in Blacks has not been adequately characterised. The pharmacokinetics of netupitant has been characterised only in Caucasians.

Renal Impairment: Mild to moderate renal impairment does not significantly affect palonosetron pharmacokinetic parameters. Total systemic exposure of palonosetron increased by approximately 28% in severe renal impairment relative to healthy subjects. Renal excretion for netupitant is negligible. The pharmacokinetics and safety of netupitant has not been studied in patients with renal impairment or chronic kidney disease. Therefore, no dose adjustment for AKYNZEO is necessary in patients with mild to moderate renal impairment. Use of AKYNZEO in patients with severe renal impairment or end-stage renal disease should be avoided.

Hepatic Impairment:

Palonosetron: Hepatic impairment does not significantly affect total body clearance of palonosetron compared to the healthy subjects. *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 of AKYNZEO 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). No dose adjustment is possible with AKYNZEO, and considerably increased exposure to netupitant can be expected in severe hepatic impairment. Therefore AKYNZEO should be used with caution in these patients.

Children: The safety and efficacy of AKYNZEO in children have not been established. No data are available.

Interactions with Other Medicines

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. Further *in vitro* studies indicated that palonosetron is not an inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2C9, CPY2D6, CYP2E1 and CYP3A4/5 (CYP2C19 was not investigated) nor does it induce the activity of CYP1A2, CYP2D6, or CYP3A4/5. Therefore, the potential for clinically significant drug interactions with palonosetron appears to be low.

Based on the *in vitro* studies, netupitant and its metabolites are unlikely to have *in vivo* drug-drug interactions via inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 at the clinical dose of 300 mg.

Netupitant and its metabolites, M1, M2 and M3, are not inducers of CYP1A2, CYP2C9, CYP2C19 and CYP3A4. When AKYNZEO is used concomitantly with another CYP3A4 inhibitor, netupitant plasma concentrations could be elevated. When AKYNZEO is used concomitantly with medications that induce CYP3A4 activity, netupitant plasma concentrations could be reduced and this may result in decreased efficacy of AKYNZEO. AKYNZEO can increase plasma concentrations of concomitantly administered medications that are metabolised via CYP3A4.

<u>Interaction Between Netupitant and Oral Palonosetron:</u>

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

<u>Interaction with CYP3A4 Substrates:</u>

Netupitant, a component of AKYNZEO, is a moderate inhibitor of CYP3A4. AKYNZEO should be used with caution in patients receiving concomitant medications that are primarily metabolised through CYP3A4. The plasma concentrations of CYP3A4 substrates can increase when co-administered

with AKYNZEO. Netupitant has a half-life of 88 hours. The inhibitory effect on CYP3A4 can last over 4 days.

Dexamethasone
Dexamethasone doses should be reduced when given with AKYNZEO (Refer to Clinical Studies, Table 1). Co-administration of a single dose of netupitant (300 mg) with a dexamethasone regimen (20 mg on Day 1, followed by 8 mg b.i.d. from Day 2 to Day 4) significantly increased the exposure to dexamethasone in a time and dose dependent manner. During the 4-day treatment period, increase of dexamethasone exposure, as expressed by the AUC, ranged from 1.7 to 2.4-fold with co-administration of 300 mg netupitant. Similarly, increase of C_{max} and C_{min} ranged from 1.1 to 1.7-fold and from 3.5 to 5.1-fold, respectively.

Interaction with Chemotherapeutic Agents (Docetaxel, Etoposide, Cyclophosphamide)
The systemic exposure of chemotherapy agents metabolised by CYP3A4 can increase when administered with AKYNZEO. Chemotherapy agents that are known to be metabolised by CYP3A4 include docetaxel, paclitaxel, etoposide, irinotecan, cyclophosphamide, ifosfamide, imatinib, vinorelbine, vinblastine, and vincristine. Exposure to docetaxel and etoposide was increased 37% and 21%, respectively, when co-administered with AKYNZEO. Caution and monitoring for chemotherapeutic related adverse reactions are advised in patients receiving chemotherapy agents metabolized primarily by CYP3A4. No consistent effect was seen with cyclophosphamide after netupitant co-administration.

Interaction with 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 in 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 of midazolam or other benzodiazepines metabolised via CYP3A4 (alprazolam, triazolam) should be considered when coadministering these agents with AKYNZEO.

Rifampicin
Single dose AKYNZEO was administered with rifampicin, a strong CYP3A4 inducer, following once daily administration of 600 mg rifampicin for 17 days. Pharmacokinetics of netupitant and palonosetron were compared to that after administration of AKYNZEO alone. Co-administration of rifampicin decreased the mean C_{max} and $AUC_{0-\infty}$ of netupitant by 62% and 82%, respectively,

compared to those after AKYNZEO alone. Co-administration of rifampicin decreased the mean C_{max} and AUC for palonosetron by 15% and 19%, respectively. Co-administration of a strong CYP3A4 inducer can therefore decrease the efficacy of AKYNZEO.

Ketoconazole
Single dose AKYNZEO was administered with ketoconazole, a strong CYP3A4 inhibitor, following once daily administration of 400 mg ketoconazole for 12 days. Pharmacokinetics of netupitant and palonosetron were compared to that after administration of AKYNZEO alone. Co-administration with ketoconazole increased mean C_{max} and AUC of netupitant by 25% and 140%, respectively, compared to those after administration of AKYNZEO alone. The mean AUC and C_{max} of palonosetron were 10% and 15% higher, respectively, when co-administered with ketoconazole. No dosage adjustment is necessary for single dose administration of AKYNZEO.

Interaction with Warfarin, Tolbutamide:

AKYNZEO interactions with CYP2C9 substrates (e.g.warfarin, tolbutamide) are unlikely. *In vitro* studies using human liver microsomes indicate that palonosetron is not an inhibitor of CYP2C9 and netupitant is not a CYP2C9 inducer or inhibitor at clinically relevant concentrations.

Effect of Other Agents on the Pharmacokinetics of AKYNZEO

Netupitant is mainly metabolised by CYP3A4; therefore, co-administration of AKYNZEO with drugs that inhibit or induce CYP3A4 activity may influence plasma concentrations of netupitant. Consequently, concomitant administration of AKYNZEO with strong CYP3A4 inhibitors (e.g. ketoconazole) or inducers (e.g., rifampin) should be approached with caution.

Additional Interactions with Palonosetron

There have been reports of serotonin syndrome following concomitant use of 5-HT_3 antagonists and other serotonergic drugs (including SSRIs and SNRIs). A study in healthy volunteers involving single-dose IV palonosetron (0.75 mg) and steady state oral metoclopramide (10 mg four times daily) demonstrated no significant pharmacokinetic interaction.

In controlled clinical trials, ALOXI injection has been safely administered with corticosteroids, analgesics, antiemetics/antinauseants, antispasmodics and anticholinergic agents.

Palonosetron did not inhibit the antitumor activity of the five chemotherapeutic agents tested (cisplatin, cyclophosphamide, cytarabine, doxorubicin and mitomycin C) in murine tumor models.

Additional Interactions with Netupitant

Based on *in vitro* studies, netupitant is an inhibitor of P-gp and BCRP transporters. In addition, metabolite M2 is a substrate for P-gp. Netupitant's potential for being a substrate for P-gp is unknown. *In vitro* studies indicate that netupitant and its three major metabolites are unlikely to have *in vivo* drug-drug interactions with human efflux transporters BSEP, MRP2, and human uptake transporters OATP1B1, OATP1B3, OAT1, OAT3, OCT1, and OCT2 at the clinical dose of 300 mg.

Adverse Effects

The safety profile of AKYNZEO was evaluated in 1169 cancer patients, including 782 exposed to AKYNZEO for at least 4 cycles and 321 exposed for at least 6 cycles, up to a maximum of 12 cycles of chemotherapy. All patients received a single oral dose of AKYNZEO one hour prior to the start of each chemotherapy cycle. In all studies, dexamethasone was co-administered with AKYNZEO (see Clinical Studies, Tables 1, 3 and 5).

Adverse reactions, considered as drug-related by the investigator, were reported in approximately 13% of patients treated with AKYNZEO. AKYNZEO was discontinued due to adverse reactions in 3.7 % of patients. The adverse reaction profile was similar across all cycles. The following is a listing of the adverse reactions reported by ≥ 1% of patients treated with AKYNZEO for one or more cycles.

Adverse Reactions Occurring in ≥1% of Cancer Patients Receiving AKYNZEO in Chemotherapy-Induced Nausea and Vomiting Studies (All Cycles)

Adverse Drug Reactions	**AKYNZEO (N=1169)**	**Palonosetron 500 mcg (N=1231)**	**Aprepitant plus $5HT_3$ (N=238)**
Nervous system Disorders			
Headache	3.6%	2.9%	1.7%
Gastrointestinal Disorders			
Constipation	3.0%	2.5%	1.3%
General Disorders			
Fatigue	1.2%	0.7%	==

The following uncommon (≥0.1% to <1%) adverse reactions were reported as treatment-related adverse events in at least two cancer patients receiving AKYNZEO in chemotherapy-induced nausea and vomiting studies:

Blood and lymphatic system disorders: leucocytosis, neutropenia

Cardiac disorders: atrioventricular block, bundle branch block, cardiomyopathy, conduction disorder

Ear and labyrinth disorders: vertigo

Gastrointestinal disorders: abdominal distension, abdominal pain, diarrhoea, dyspepsia, flatulence, nausea

General disorders and administration: asthenia

Investigations: liver transaminases increased, blood alkaline phosphatase increased, blood creatine phosphokinase increased, blood creatinine increased, electrocardiogram QT prolonged, electrocardiogram ST -T abnormal

Metabolism and nutrition disorders: decreased appetite

Nervous system disorders: dizziness

Psychiatric disorders: insomnia

Respiratory, thoracic and mediastinal disorders: hiccups

Skin and subcutaneous tissue disorders: alopecia, urticaria

Vascular disorders: hypertension

Post Marketing Experience:

There is no post marketing data available at this time.

Dosage and Administration

Method of Administration

One AKYNZEO 300 mg/500 mcg capsule should be administered approximately one hour prior to the start of each chemotherapy cycle.

To be taken orally.

The hard capsule should be swallowed whole.

AKYNZEO can be taken with or without food.

The concomitant use of dexamethasone is recommended.

The recommended oral dexamethasone dose should be reduced by approximately 50 % when co-administered with Akynzeo (see Table 1 and Table 3 of the *Clinical Study* section).

Elderly Population

No dosage adjustment is necessary for elderly patients.

Paediatric Population

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

Patients with Renal Impairment

Dosage adjustment for AKYNZEO is not considered necessary in patients with mild to moderate renal impairment. Use of AKYNZEO in patients with severe renal impairment or end-stage renal disease should be avoided (see *Precautions: Special populations*).

Patients with 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), therefore AKYNZEO should be used with caution in these patients.

Overdosage

No case of overdose has been reported and 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 the unlikely event of overdose, AKYNZEO 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 AKYNZEO overdose.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

Presentation and Storage Conditions

Presentation:

AKYNZEO is supplied as a hard, opaque, gelatin capsule with white body and caramel cap with “HE1” printed on the body.

Each carton contains an aluminium/aluminium blister containing one hard capsule.

300 mg / 500 mcg: AUST R 222237

Storage:

Store below 25°C.
Store in the original container in order to protect from light.

Name and Address of Sponsor

Specialised Therapeutics Australia Pty Ltd
Level 1, 711 High Street
Kew East Victoria 3102
Australia

Tel: 1300 798 820
Fax: 1800 798 829

Poison Schedule of the Medicine:

Prescription Only Medicine (S4)

Date of First Inclusion in the ARTG

06 May 2015

Date of the Most Recent Amendment