PRODUCT MONOGRAPH

Pr Akynzeo®

netupitant / palonosetron capsules

300 mg netupitant / 0.5 mg palonosetron (as palonosetron hydrochloride)

Antiemetic
(NK_1 receptor antagonist/5-HT_3 receptor antagonist)

A04AA55

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[Pr]Akynzeo®

netupitant / palonosetron capsules

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Non-medicinal Ingredients
Oral	Capsule: 300 mg / 0.5 mg netupitant / palonosetron (as palonosetron hydrochloride)	Glycerol monocaprylocaprate, microcrystalline cellulose, sucrose lauric acid esters, povidone K-30, croscarmellose sodium, colloidal hydrated silica, sodium stearyl fumarate, magnesium stearate, glycerin, polyglyceryl dioleate, purified water, butylhydroxyanisole, gelatin, sorbitol, 1,4 sorbitan, titanium dioxide, shellac glaze (partially esterified), yellow, red and black iron oxide, propylene glycol. May contain traces of lecithin derived from soya, medium-chain triglycerides, and denatured ethanol.

INDICATIONS AND CLINICAL USE

Akynzeo® (netupitant/palonosetron) in combination with dexamethasone, is indicated for once-per-cycle treatment in adult patients for:

- Prevention of acute and delayed nausea and vomiting associated with highly emetogenic cancer chemotherapy
- Prevention of acute nausea and vomiting associated with moderately emetogenic cancer therapy that is uncontrolled by a 5-HT_3 receptor antagonist alone

Geriatrics (≥ 65 years of age):
No dosage adjustment is required in patients ≥ 65 years of age and older. In general, use caution when dosing geriatric patients as they have a greater frequency of decreased hepatic, renal or cardiac function and concomitant disease or other drug therapy.

Pediatrics (< 18 years of age):
The safety and effectiveness of **Akynzeo** in patients below the age of 18 years have not been established. No data are available.

CONTRAINDICATIONS

- **Akynzeo®** (netupitant/palonosetron) is contraindicated in patients who are hypersensitive to these drugs or to any ingredient in the formulation or component of the container. For a complete listing, see **DOSAGE FORMS, COMPOSITION AND PACKAGING**.
- **Akynzeo** is contraindicated during pregnancy.
- **Akynzeo** should not be used concurrently with pimozide, terfenadine, astemizole, or cisapride. Inhibition of cytochrome P450 isoenzyme 3A4 (CYP3A4) by netupitant could result in elevated plasma concentrations of these drugs, potentially causing serious or life-threatening reactions (see **DRUG INTERACTIONS**).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Drug interactions may occur with medicinal products, including chemotherapeutic agents (see **WARNINGS AND PRECAUTIONS**) that are metabolized through **CYP3A4** (see **DRUG INTERACTIONS**).

General

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.

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 signs of an allergic reaction.

Carcinogenesis and Mutagenesis

Long-term studies in animals to evaluate carcinogenic potential have not been performed with netupitant. Netupitant was not genotoxic in the Ames test, the mouse lymphoma cell mutation test, or the *in vivo* rat micronucleus test (see **TOXICOLOGY**, **Genotoxicity**).

Statistically significant increased incidences of a variety of different tumors affecting the adrenal, liver, mammary gland, and other tissues and organs were observed at high doses of palonosetron in a rat carcinogenicity study. In the mouse study, the findings were not attributed to palonosetron treatment (see **TOXICOLOGY**, **Carcinogenicity**). Experimental evidence indicates that palonosetron is non-mutagenic (see **TOXICOLOGY**, **Genotoxicity**).

Cardiac/QTc prolongation

An ECG assessment study was conducted in adult male and female healthy subjects with oral netupitant 200 or 600 mg administered in combination with oral palonosetron 0.5 or 1.5 mg respectively. A small QTc prolongation effect was observed, averaging up to approximately 4 ms (200/0.5 mg) and 6 ms (600/1.5 mg) (see **ACTION AND CLINICAL PHARMACOLOGY**, **Pharmacodynamics**).

Many drugs that cause QTc prolongation are suspected to increase the risk of torsade de pointes, a polymorphic ventricular tachyarrhythmia that may be asymptomatic or experienced by the patient as dizziness, palpitations, syncope, or seizures. If sustained, torsade de pointes can progress to ventricular fibrillation and sudden cardiac death.

Caution should be exercised in patients who have or are likely to develop prolongation of the QT interval. Risk factors include, but are not limited to, a personal or family history of QT prolongation (e.g., congenital long QT syndromes), electrolyte abnormalities or conditions that can lead to electrolyte abnormalities (e.g., eating disorders), cardiac disease (e.g., congestive heart failure, myocardial ischemia, conduction system disease), and bradycardia or bradyarrhythmia. Caution should also be observed in patients taking anti-arrhythmic medicinal products, other medicinal products that lead to QT prolongation or electrolyte abnormalities, or drugs that inhibit the metabolism of netupitant or palonosetron (see **DRUG INTERACTIONS**). Hypokalemia, hypocalcemia, and hypomagnesemia should be corrected prior to administration.

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). 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.

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.

Hypersensitivity

Hypersensitivity reactions, including anaphylaxis, have been reported with or without known hypersensitivity to other 5-HT_3 receptor antagonists.

Psychomotor Impairment

Akynzeo may influence 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 until they know how they react to **Akynzeo**.

Serotonin Syndrome/Neuroleptic Malignant Syndrome-like Events

Cases of life-threatening serotonin syndrome or neuroleptic malignant syndrome-like events have been reported with 5-HT_3 receptor antagonist antiemetics, particularly when given in combination with other serotonergic and/or neuroleptic drugs. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

As these syndromes may result in potentially life-threatening conditions, treatment should be discontinued if such events occur and supportive symptomatic treatment should be initiated. If

concomitant treatment of **Akynzeo** with a drug affecting the serotonergic neurotransmitter system is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see **DRUG INTERACTIONS**).

Special Populations

Women of Childbearing Potential/Contraception in Women:

Pregnant women or women intending to become pregnant should not take **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.

Pregnant Women:

Akynzeo is contraindicated in pregnancy.

There are no data from the use of netupitant in pregnant women. Studies of netupitant in animals have shown reproductive toxicity, including teratogenic effects in rabbits at exposures lower than the recommended single dose in humans (see **TOXICOLOGY**, **Reproductive Toxicity**).

There are no data from 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 **TOXICOLOGY**, **Reproductive Toxicity**).

Nursing Women:

It is not known whether netupitant or palonosetron are present in human milk. Because many drugs are present in human milk and because of the potential for tumorigenicity shown for palonosetron in the rat carcinogenicity study (see **TOXICOLOGY**), **Akynzeo** should not be used in women who are breast-feeding and for 1 month after the last dose.

Geriatrics (≥ 65 years of age):

No dosage adjustment is required in patients ≥ 65 years of age. In general, use caution when dosing geriatric patients as they have a greater frequency of decreased hepatic, renal or cardiac function and concomitant disease or other drug therapy.

Pediatrics (< 18 years of age):

The safety and effectiveness of **Akynzeo** in patients below the age of 18 years have not been established and no data are available.

Hepatic Impairment

No dosage adjustment of **Akynzeo** is necessary in patients with mild to moderate hepatic impairment (Child-Pugh score 5 to 9). Limited data exist on the use of **Akynzeo** in patients with severe hepatic impairment (Grade C, Child-Pugh score > 9). Avoid use of **Akynzeo** in patients with severe hepatic impairment because of the potential for increased exposure to netupitant (see **ACTION AND CLINICAL PHARMACOLOGY**, **Special Populations and Conditions**, **Hepatic Impairment**).

Renal Impairment

No dosage adjustment of **Akynzeo** is necessary in patients with mild to moderate renal impairment. The pharmacokinetics of palonosetron and netupitant has not been studied in patients with severe or end-stage renal disease requiring hemodialysis and no data on the effectiveness or safety of **Akynzeo** in these patients are available. Avoid use of **Akynzeo** in patients with severe or end-stage renal disease (see **ACTION AND CLINICAL PHARMACOLOGY**, **Special Populations and Conditions**, **Renal Impairment**).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The most common adverse events reported with **Akynzeo®** in clinical trials were headache (3.6%), constipation (3.0%) and fatigue (1.2%).

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Cisplatin-based Chemotherapy (Cycle 1)

In a single-cycle study of patients receiving cisplatin-based highly emetogenic chemotherapy (NETU-07-07), 136 patients were treated with **Akynzeo**. Table 1 shows TEAEs defined as adverse events reported at an incidence of ≥ 2% in **Akynzeo** in comparison to palonosetron alone.

Table 1: Treatment Emergent Adverse Events Occurring in ≥ 2% ¡Error! No se encuentra el origen de la referencia. **of Cancer Patients Receiving Akynzeo and Cisplatin Based Highly Emetogenic Chemotherapy (Cycle 1) (Study NETU-07-07)**

System Organ Class Preferred Term	netupitant 300 mg / palonosetron 0.5 mg (n=136) n (%)	palonosetron 0.5 mg (n=136) n (%)
Blood and Lymphatic System Disorders		
Leukocytosis	5 (3.7)	10 (7.4)
Lymphocytosis	3 (2.2)	1 (0.7)
Neutrophilia	5 (3.7)	4 (2.9)
Cardiac Disorders		
Bundle branch block	3 (2.2)	-
Gastrointestinal Disorders		
Abdominal pain upper	3 (2.2)	2 (1.5)
Constipation	4 (2.9)	1 (0.7)
Dyspepsia	6 (4.4)	2 (1.5)

Table 1: Treatment Emergent Adverse Events Occurring in ≥ 2% ¡Error! No se encuentra el origen de la referencia. **of Cancer Patients Receiving Akynzeo and Cisplatin Based Highly Emetogenic Chemotherapy (Cycle 1) (Study NETU-07-07)**

System Organ Class Preferred Term	netupitant 300 mg / palonosetron 0.5 mg (n=136) n (%)	palonosetron 0.5 mg (n=136) n (%)
General Disorders		
Asthenia	12 (8.8)	13 (9.6)
Fatigue	6 (4.4)	3 (2.2)
Investigations		
Alanine aminotransferase increased	9 (6.6)	9 (6.6)
Aspartate aminotransferase increased	6 (4.4)	5 (3.7)
Blood urea increased	3 (2.2)	9 (6.6)
Metabolism and Nutrition Disorders		
Anorexia	5 (3.7)	11 (8.1)
Nervous System Disorders		
Headache	5 (3.7)	9 (6.6)
Respiratory Disorders		
Hiccups	7 (5.1)	7 (5.1)
Skin and Subcutaneous Tissue Disorders		
Erythema	4 (2.9)	2 (1.5)
Vascular disorders		
Hypertension	3 (2.2)	1 (0.7)

a. (%) = number (percentage) of patients with at least one event for each SOC and PT

Anthracycline and Cyclophosphamide-Based Chemotherapy (Cycle 1)

In a study of patients receiving anthracycline and cyclophosphamide based chemotherapy (study NETU-08-18), 725 patients were treated with **Akynzeo** during Cycle 1, and 635 of these patients continued for up to 8 cycles in a multiple-cycle extension. Table 2 shows TEAEs defined as adverse events reported at an incidence of ≥2% in **Akynzeo** in comparison to palonosetron alone during Cycle 1 (see Table 2). The percentage of patients who reported at least 1 TEAE was highest at cycle 1 and decreased by cycle through cycle 6 in the netupitant/palonosetron group and the palonosetron group, except between cycle 4 and cycle 5 in the netupitant/palonosetron group (1.6%, 5/317 patients and 2.2%, 7/317 patients).

Table 2: Treatment Emergent Adverse Events Occurring in ≥ 2%[a] of Cancer Patients Receiving Akynzeo and Anthracyclines and Cyclophosphamide Based Chemotherapy (Cycle 1) (Study NETU-08-18)

System Organ Class Preferred Term	netupitant 300 mg / palonosetron 0.5mg (n=725) n (%)	palonosetron 0.5mg (n=725) n (%)
Blood and Lymphatic System Disorders		
Anemia	26 (3.6)	24 (3.3)
Leukopenia	96 (13.2)	90 (12.4)
Lymphopenia	21 (2.9)	14 (1.9)
Neutropenia	173 (23.9)	182 (25.1)

Table 2: Treatment Emergent Adverse Events Occurring in ≥ 2%[a] of Cancer Patients Receiving Akynzeo and Anthracyclines and Cyclophosphamide Based Chemotherapy (Cycle 1) (Study NETU-08-18)

System Organ Class Preferred Term	netupitant 300 mg / palonosetron 0.5mg (n=725) n (%)	palonosetron 0.5mg (n=725) n (%)
Gastrointestinal Disorders		
Constipation	31 (4.3)	26 (3.6)
Nausea	22 (3.0)	27 (3.7)
Stomatitis	17 (2.3)	9 (1.2)
General Disorders		
Asthenia	59 (8.1)	50 (6.9)
Fatigue	47 (6.5)	38 (5.2)
Metabolism and Nutrition Disorders		
Decreased appetite	25 (3.4)	32 (4.4)
Hyperglycemia	24 (3.3)	25 (3.4)
Nervous System Disorders		
Dizziness	15 (2.1)	11 (1.5)
Headache	64 (8.8)	52 (7.2)
Skin and Subcutaneous Tissue Disorders		
Alopecia	253 (34.9)	253 (34.9)

a. (%) = number and percentage of patients affected (patients with multiple events counted only once per line)

Multiple-Cycle Safety Study in Patients receiving Carboplatin, Cisplatin, Oxaliplatin, or Doxorubicin

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). No new safety issues were identified.

Less Common Clinical Trial Adverse Drug Reactions

In pivotal clinical trials, the following TEAEs occurring at a rate of < 2% in **Akynzeo** patients were reported:

Blood and lymphatic system disorders: Febrile neutropenia, thrombocytopenia

Cardiac disorders: Palpitations, supraventricular extrasystoles, tachycardia, ventricular extrasystoles

Gastrointestinal disorders: Abdominal pain, diarrhea, dry mouth,

General disorders and administration site conditions: Pyrexia

Investigations: Blood bilirubin increased, blood creatine phosphokinase increased, blood glucose increased, blood pressure

	decreased, blood pressure increased, electrocardiogram QT prolonged, neutrophil count increased, white blood cell count increased
Metabolism and nutrition disorders:	Hyponatremia
Musculoskeletal and connective tissue disorders:	Back pain
Nervous system disorders:	Dysguesia
Psychiatric disorders:	Insomnia
Renal and urinary disorders:	Proteinuria

Abnormal Hematologic and Clinical Chemistry Findings

The reports of concomitant elevations of transaminases > 3 x ULN, and total bilirubin in both arms of the Phase III trials that compared **Akynzeo** to oral palonosetron, were comparable in frequency between the treatment groups (see Table 3).

Table 3: Liver Function Laboratory Abnormalities

Laboratory Changes	netupitant 300mg / palonosetron 0.5mg (n = 861)	palonosetron 0.5mg (n = 861)
AST > 3 x ULN and/or ALT > 3 x ULN with Total Bilirubin > ULN	3 (0.3%)	5 (0.6%)
AST > 10 x ULN and/or ALT > 10 x ULN with Total Bilirubin > ULN	-	2 (0.2%)
AST > 3 x ULN and/or ALT > 3 x ULN with Total Bilirubin ≥ 2 x ULN	1 (0.1%)	1 (0.1%)

DRUG INTERACTIONS

Serious Drug Interactions

- **Akynzeo**® should be used with caution in patients receiving concomitant medications that are primarily metabolized through CYP3A4, including chemotherapy agents. Inhibition of CYP3A4 by netupitant could result in elevated plasma concentrations of these concomitant medications, and can last for multiple days (see **CONTRAINDICATIONS** and **DRUG INTERACTIONS, Drug-Drug Interactions**).

Overview

Netupitant is a substrate and moderate inhibitor of CYP3A4.

The potential drug interactions listed below are not comprehensive. Drugs that prolong the QTc interval, decrease electrolytes, or inhibit CYP3A4 should be avoided (See **WARNINGS AND PRECAUTIONS**, **Cardiac/QTc Prolongation** and **ACTION AND CLINICAL PHARMACOLOGY**, **Pharmacodynamics**, **Cardiac Electrophysiology**).

Drug-Drug Interactions

QTc Interval-Prolonging Drugs

Caution should be observed if **Akynzeo** is used concomitantly with other QTc interval-prolonging drugs. Drugs that have been associated with QTc interval prolongation and/or torsade de pointes include, but are not limited to: Class IA, III, IC antiarrhythmics, antipsychotics, antidepressants, opioids, macrolide antibiotics and analogues, quinolone antibiotics, pentamidine, antimalarials, azole antifungals, domperidone, 5-HT_3 receptor antagonists, tyrosine kinase inhibitors, arsenic trioxide, histone deacetylase inhibitors and beta-2 adrenoceptor agonists.

Drugs that Affect Electrolytes

Caution should be observed if **Akynzeo** is used with drugs that can decrease electrolyte levels, which include, but are not limited to, the following: loop, thiazide, and related diuretics; laxatives and enemas; amphotericin B; high-dose corticosteroids; and proton pump inhibitors.

Interaction with CYP3A4 Inhibitors

Netupitant is a substrate for CYP3A4. Plasma levels of netupitant can be increased by inhibitors of CYP3A4. Strong inhibitors of CYP3A4 include, but are not limited to, ketoconazole, itraconazole, clarithromycin, indinavir, nelfinavir, and ritonavir. The concomitant use of these drugs with netupitant is not recommended.

Interaction with CYP3A4 Substrates

Akynzeo (netupitant/palonosetron) should be used with caution in patients receiving concomitant medications, including chemotherapeutic agents that are primarily metabolized through CYP3A4. The plasma concentrations of CYP3A4 substrates can increase when co-administered with **Akynzeo**. The inhibitory effect on CYP3A4 can last for multiple days. Caution and careful monitoring are advised in patients receiving chemotherapy agents metabolized by CYP3A4 (see **WARNINGS AND PRECAUTIONS**).

Based on *in vitro* studies, palonosetron is mainly metabolised by CYP2D6 and to a lesser extent by CYP3A4 and CYP1A2 isoenzymes. Palonosetron does not inhibit or induce cytochrome P450 isoenzymes at clinically relevant concentrations (CYP2C19 was not investigated). See **ACTION AND CLINICAL PHARMACOLOGY**, **Pharmacokinetics**, **Metabolism**.

Table 4: Established or Potential Drug-Drug Interactions with Akynzeo

Drug/Drug Class	Ref	Effect	Clinical Comment
Pimozide	T	Increased pimozide concentration	Potentially causing serious or life-threatening reactions.
Terfenadine	T	Increased terfenadine concentration	Potentially causing serious or life-threatening reactions.

Table 4: Established or Potential Drug-Drug Interactions with Akynzeo

Drug/Drug Class	Ref	Effect	Clinical Comment
Astemizole	T	Increased astemizole concentration	Potentially causing serious or life-threatening reactions.
Cisapride	T	Increased cisapride concentration	Potentially causing serious or life-threatening reactions.
Dexamethasone	CT[a]	Single dose of netupitant caused a two-fold increase in dexamethasone AUC. The PK profile of netupitant was unchanged when administered in combination with dexamethasone.	50% reduction of dexamethasone dose recommended
Docetaxel	CT	Co-administration with **Akynzeo** caused a 35% increase in docetaxel AUC.	Caution and monitoring for adverse reactions in patients receiving chemotherapeutic agents metabolized by CYP3A4.
Etoposide	CT	Co-administration with **Akynzeo** caused a 28% increase in etoposide AUC.	Caution and monitoring for adverse reactions in patients receiving chemotherapeutic agents metabolized by CYP3A4.
Cyclophosphamide	CT	Co-administration with netupitant showed no consistent effect.	Caution and monitoring for adverse reactions in patients receiving chemotherapeutic agents metabolized by CYP3A4.
Erythromycin	CT	Co-administration of netupitant caused a 1.3-fold increase in erythromycin AUC. Netupitant pharmacokinetics unaffected.	Not considered clinically significant.
Midazolam	CT	Co-administration of netupitant caused a 2.4-fold increase in midazolam AUC. Netupitant pharmacokinetics unaffected.	Not considered clinically significant. Consider potential effects of increased AUC for midazolam or other benzodiazepines metabolized by CYP3A4 (e.g. alprazolam, triazolam). Not considered clinically significant.
Oral contraceptives (ethinylestradiol, levonorgestrel)	CT	Co-administration with **Akynzeo** caused a 1.4-fold increase in levonorgestrel AUC. No significant effect on ethinylestradiol. Netupitant and palonosetron pharmacokinetics unaffected.	Clinically relevant effects on hormonal contraception unlikely.

Table 4: Established or Potential Drug-Drug Interactions with Akynzeo

Drug/Drug Class	Ref	Effect	Clinical Comment
CYP3A4 Inducers (e.g. rifampin)	CT	Presence of rifampin caused a 5.2-fold decrease in netupitant AUC. Palonosetron pharmacokinetics unaffected.	Concomitant use of **Akynzeo** should be avoided in patients using strong CYP3A4 inducers.
CYP3A4 Inhibitors (e.g. ketoconazole)	CT	Presence of ketoconazole caused a 1.8-fold increase in netupitant AUC. No effect on palonosetron.	Caution is recommended if **Akynzeo** is coadministered with strong CYP3A4 inhibitors.
P-gp Substrates (e.g. digoxin)	CT	*In vitro* data shows that netupitant is a P-gp inhibitor. Netupitant did not affect the AUC of digoxin but increased the C_{max} by 1.09-fold.	This inhibitory 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.
Serotonergic Drugs	C[a]	Reports of serotonin syndrome with concomitant use of 5-HT_3 antagonists and other serotonergic drug products (including SSRIs and SNRIs).	Caution recommended if Akynzeo combined with other serotonergic drug products.
UGT2B7 Substrates (e.g. zidovudine, valproic acid, morphine)	IV	*In vitro* data indicates that netupitant inhibits UGT2B7.	Clinical relevance is unknown. Caution recommended if **Akynzeo** is combined with an oral substrate of this enzyme.

a. CT = Clinical Trial
b. C = Case Study
c. T = Theoretical
d. IV = *In Vitro*

In vitro data suggests that netupitant might inhibit the efflux of transporter Breast Cancer Resistance Protein (BCRP) and P-glycoprotein (P-gp) transporters. The clinical relevance of this effect is not established for BCRP. A clinical study with digoxin indicated no clinically relevant interaction of netupitant with P-gp.

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

Drug-Food Interactions

As a potent inhibitor of intestinal CYP3A4, grapefruit or grapefruit juice should be avoided during treatment with **Akynzeo** (see **DRUG INTERACTIONS**, **Drug-Drug Interactions**).

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations
Akynzeo® (netupitant/palonosetron) is for oral administration. One capsule, per chemotherapy cycle.

The recommended oral dexamethasone dose should be reduced by approximately 50 % when coadministered with **Akynzeo** (see **DRUG INTERACTIONS, Drug-Drug Interactions**).

Akynzeo should be swallowed whole.

Akynzeo can be taken with or without food.

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

Recommended Dosage and Administration
Highly Emetogenic Chemotherapy, including Cisplatin Based Chemotherapy
Day 1: 1 capsule of **Akynzeo** administered orally approximately 1 hour prior to the start of each chemotherapy cycle with dexamethasone 12 mg to be administered orally 30 minutes prior to chemotherapy
Day 2 to 4: dexamethasone 8 mg orally once daily

For Anthracycline and Cyclophosphamide-Based Chemotherapy and for Chemotherapy Not Considered to be Highly Emetogenic
Day 1: 1 capsule of **Akynzeo** administered orally approximately 1 hour prior to the start of each chemotherapy cycle with dexamethasone 12 mg to be administered orally 30 minutes prior to chemotherapy.
Day 2 to 4: administration of dexamethasone on days 2 to 4 is not necessary.

Hepatic Impairment:
No dosage adjustment of **Akynzeo** is necessary in patients with mild to moderate hepatic impairment (Child-Pugh score 5 to 9). Limited data exist on the use of **Akynzeo** in patients with severe hepatic impairment (Grade C, Child-Pugh score > 9) but because of the potential for increased exposure to netupitant, use should be avoided in these patients (see **WARNINGS AND PRECAUTIONS, Hepatic Impairment** and **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Hepatic Impairment**).

Renal Impairment:
No dosage adjustment of **Akynzeo** is necessary in patients with mild to moderate renal impairment. The pharmacokinetics of **Akynzeo** has not been studied in patients with severe or end-stage renal disease requiring hemodialysis. Therefore, use in these patients should be

avoided (see **WARNINGS AND PRECAUTIONS, Renal Impairment** and **ACTION AND CLINICAL PHARMACOLOGY**, **Special Populations and Conditions**, **Renal Impairment**).

Pediatric Population (<18 years old):

The safety and efficacy of **Akynzeo** in the pediatric population have not been established. No data are available.

Geriatrics (> 65 years old):

No dosage adjustment is required in patients ≥ 65 years of age (see **ACTION AND CLINICAL PHARMACOLOY**, **Special Populations and Conditions**, **Use in Geriatric Patients**). In general, use caution when dosing elderly patients as they have a greater frequency of decreased hepatic, renal or cardiac function and concomitant disease or other drug therapy.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

No specific information is available on the treatment of overdose with **Akynzeo®** and there is no known antidote.

In case 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 overdose.

Fifty adult cancer patients were administered oral palonosetron at a dose of 90 µg/kg (equivalent to 6 mg fixed dose in a 70 kg individual) as part of a dose ranging study. This is approximately 12 times the recommended oral dose of 0.5 mg. This dose group had a similar incidence of adverse events compared to the other dose groups and no dose response effects were observed.

The highest dose of netupitant administered to 1169 cancer patients was 300 mg. The highest dose of netupitant administered to 49 healthy subjects was 600 mg. A similar incidence of adverse events was observed when compared to lower doses of netupitant in the respective populations of cancer patients and healthy subjects.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Akynzeo™, a fixed dose combination of netupitant and palonosetron, has a dual mode of action targeting both the 5-HT_3 and NK_1 receptor neuropathways.

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

Palonosetron is a 5-HT_3 receptor antagonist with a strong binding affinity for this receptor and little or no affinity for other receptors. Chemotherapeutic substances produce nausea and vomiting by stimulating the release of serotonin from the enterochromaffin cells of the small intestine. Serotonin then activates 5-HT3 receptors located on vagal afferents to initiate the vomiting reflex.

Pharmacodynamics

Cardiac Electrophysiology

Palonosetron: The effect of palonosetron alone on the QTc interval was evaluated in a double-blind, randomized, parallel group, placebo- and positive-controlled trial in healthy subjects (42-46/treatment group) who received single intravenous doses of palonosetron 0.25 mg, 0.75 mg, and 2.25 mg. There was a dose-dependent increase from baseline QTcI value on Day 1. In the palonosetron 0.75 mg group, there was a statistically significant difference from placebo in mean change from baseline QTcI of 3.39 ms (90% CI 0.06, 6.72) at 1 h post-dosing. In the palonosetron 2.25 mg dose group, statistically significant QTc prolongation was observed from 15 min to 2 h post-dosing, with a maximum difference from placebo of 4.78 ms (90% CI 1.44, 8.11) at 1 h.

Netupitant/Palonosetron Combination: Non-clinical studies indicate that the combination of netupitant and palonosetron may block ion channels involved in ventricular de- and re-polarization and prolong action potential duration; this effect was associated with concomitant bradycardia. A randomized, double-blind, placebo- and positive controlled, parallel group, single dose ECG assessment study was conducted in healthy subjects (N=48-49/treatment group) with two oral combination treatments: a) 200 mg netupitant/0.50 mg palonosetron and b) 600 mg netupitant/1.5 mg palonosetron. The largest point estimates of the placebo and baseline corrected QTcF ($QTcF=QT/RR^{0.33}$) interval were 4.39 ms (90% CI 2.47, 6.31) at 14 h after administration of 200 mg netupitant/0.50 mg palonosetron treatment and 5.8 ms (90% CI 3.98, 7.62) at 16 hours after the administration of 600 mg netupitant/1.5 mg palonosetron.

Both of the netupitant/palonosetron treatment groups were associated with reductions in heart rate. Statistically significant differences from placebo in mean change from baseline heart rate were observed from 1-36 h post-dosing in both netupitant/palonosetron treatment groups, with the placebo-adjusted changes from baseline heart rate averaging -2 to -6 bpm over the observation period.

NK1 Receptor Occupancy: The receptor occupancy for the CINV dosing regimen of netupitant was measured in a human Positron Emission Tomography (PET) study. Netupitant was shown to cross the blood brain barrier with a NK1 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.

Pharmacokinetics

After single dose administration of **Akynzeo** in healthy subjects under fasted conditions, the

peak plasma concentrations for netupitant and palonosetron were reached in about 5 hours (see Table 5).

Table 5: PK Parameters (mean and CV%) After Single Dose Administration of Akynzeo in Healthy Subjects

	Netupitant	Palonosetron
C_{max} (ng/mL)	434 (56)	1.53 (25)
T_{max}[a] (h)	5 (2-12)	5 (1-12)
AUC (ng*h/mL)	14401 (51)	56.7 (33)
$T_{1/2}$ (h)	96 (61)	44 (34)

a. median (min-max)

When administered under fed condition, the systemic exposure to netupitant and palonosetron was similar to those obtained under fasting condition.

In cancer patients who received a single dose of **Akynzeo** one hour prior to chemotherapy (docetaxel, etoposide, or cyclophosphamide), the C_{max} and AUC of netupitant and its metabolites were similar to those in healthy subjects. The mean C_{max} and AUC of palonosetron in cancer patients were similar to those in healthy subjects.

Absorption:

Netupitant

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 greater than dose proportional increase in C_{max} and AUC parameters with dose increases from 10 mg to 300 mg, and a dose-proportional increase in C_{max} and AUC from 300 mg to 450 mg.

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.

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%.

Palonosetron

Following oral administration, palonosetron is well absorbed with an absolute bioavailability of 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 major metabolites (M1, M2, M3) is > 97-99% at concentrations ranging from 10 to 1500 ng/mL.

Palonosetron

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

Metabolism:

Netupitant

At oral doses of 30 mg and higher netupitant is extensively metabolized to: the desmethyl derivative, M1; the N-oxide derivative, M2; the OH-methyl derivative, M3. *In vitro* studies indicate 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; Mean AUC for M1, M2 and M3 were 29% and 14% and 33%, respectively, relative to the parent. All three netupitant metabolites were shown to be pharmacologically active at the NK_1 receptor in an animal pharmacodynamic model, where M3 was the most potent and M2 the least active.

Palonosetron

Palonosetron is eliminated by multiple routes with approximately 50% metabolized to form two primary metabolites: N-oxide-palonosetron and 6-S-hydroxy-palonosetron. These metabolites each have less than 1% of the 5-HT_3 receptor antagonist activity of palonosetron. *In vitro* 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 and mean systemic clearance of 20 L/h.

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 [^{14}C]-netupitant was recovered from urine and feces 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 feces. 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 and Conditions:

Gender:

Netupitant
In a pooled analysis, the C_{max} for netupitant was 35% higher in females than in males while the AUC was similar between males and females.

Palonosetron
In female subjects, the mean AUC for palonosetron was 35% higher and the mean C_{max} was 26% higher than in male subjects.

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 (Grade A, Child-Pugh score 5 to 6) and 70%, 88% and 143% higher in moderate hepatically-impaired subjects (Grade B, Child-Pugh score 7 to 9), respectively. Limited data exist in patients with severe hepatic impairment (Grade C, Child-Pugh score > 9).

Palonosetron

Hepatic impairment does not significantly affect total body clearance of palonosetron compared to the healthy subjects. In patients with mild or moderate hepatic impairment, the mean $AUC_{0-\infty}$ of palonosetron was 33% and 62% higher, respectively, than in healthy subjects. The mean Cmax for palonosetron was about 14% higher and unchanged with mild or moderate hepatic impairment compared to 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, a 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. In a population PK study, patients with mild or moderate renal impairment also had a reduced palonosetron clearance, but this reduction did not result in a significant change in palonosetron exposure. The systemic exposure (AUC_{0-t}) to a single dose of intravenous palonosetron increased by approximately 45% in subjects with severe renal impairment relative to healthy subjects. Longer terminal half-lives (estimated 115-300 hours) were reported in 3 out of 7 patients with severe renal impairment compared to ~39 hours in healthy volunteers.

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

Use in Geriatric Patients:

In cancer patients receiving **Akynzeo**, population pharmacokinetic analysis indicated that age (within the range of 29 to 75 years old) did not influence the pharmacokinetics of netupitant or palonosetron. In healthy geriatric 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).

Of the 1169 adult cancer patients treated with **Akynzeo** in clinical studies, 18% were aged 65 and over and 2% were aged 75 years and over.

STORAGE AND STABILITY

Store at 15-30°C.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms

Akynzeo® is a combination product of 300 mg netupitant and 0.5 mg palonosetron.

Each **Akynzeo** (300 mg netupitant/0.5 mg palonosetron) capsule is composed of one white-caramel hard gelatin capsule which contains three tablets each containing 100 mg netupitant and one gelatin capsule containing 0.56 mg palonosetron hydrochloride (equivalent to 0.50 mg palonosetron). Each capsule has a white body and caramel cap with "HE1" printed on the body.

Composition

Non-medicinal ingredients:

Glycerol monocaprylocaprate, microcrystalline cellulose, sucrose lauric acid esters, povidone K-30, croscarmellose sodium, colloidal hydrated silica, sodium stearyl fumarate, magnesium stearate, glycerin, polyglyceryl dioleate, purified water, butylated hydroxyanisole (BHA), gelatin, sorbitol, 1,4 sorbitan, titanium dioxide, shellac glaze (partially esterified), yellow, red and black iron oxide, propylene glycol. May contain traces of lecithin derived from soya, medium-chain triglycerides, and denatured ethanol.

Packaging

Pack of one capsule in one blister.

Pack of four capsules (two capsules per blister strip).

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substances

Common name: netupitant

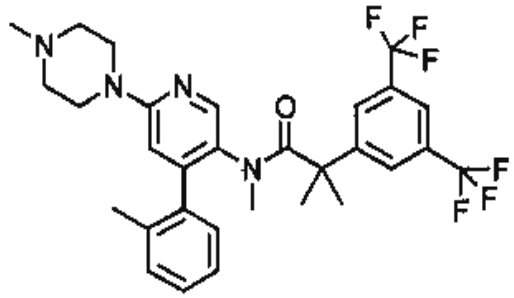
Chemical name: 2-[3,5-bis(trifluoromethyl)phenyl]-N, 2 dimethyl-N-[4-(2methylphenyl)-6-(4-methylpiperazin-1-yl)pyridin-3-yl] propanamide.

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

Molecular mass: 578.61 g/mol

Structural formula:

Figure 1: Structural formula – netupitant



Physicochemical properties: Netupitant is a white to off-white crystalline powder. It is freely soluble in toluene and acetone, soluble in isopropanol and ethanol, and very slightly soluble in water.

Proper name: palonosetron hydrochloride

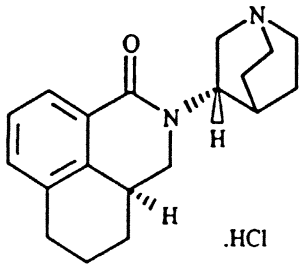
Chemical name: (3aS)-2-[(S)-1-Azabicyclo [2.2.2]oct-3-yl]-2,3,3a,4,5,6-hexahydro-1-oxo-1*H*benz[*de*]isoquinoline hydrochloride

Molecular formula: $C_{19}H_{24}N_2O \cdot HCl$

Molecular mass: 332.87 g/mol

Structural formula:

Figure 2: Structural formula - palonosetron hydrochloride



Physicochemical properties: Palonosetron hydrochloride is a white to off-white crystalline powder. It is freely soluble in water, soluble in propylene glycol, and slightly soluble in ethanol and 2- propanol.

CLINICAL TRIALS

Oral administration of **Akynzeo**® (netupitant/palonosetron) in combination with dexamethasone has been shown to prevent acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic chemotherapy in two controlled clinical trials. The primary efficacy endpoint in each study was complete response (CR) rate (defined as no emetic episodes, no rescue medication) within 120 hours (5 days) (overall phase) after the start of the highly emetogenic chemotherapy administration.

Table 6: Study Demographics and Trial Design

Study ID Number	Design Control Type	Study & Control Drugs	Number of Subjects by Arm (Total Treated/ FAS)	Duration	Gender M/F Median Age Range (years)	Chemotherapy Regimen
NETU-07-07	Randomized (1:1:1:1:1) double-blind, parallel	Palonosetron 0.5mg po	136/136	1 cycle	387 M 292 F 55.0 (19-82)	cisplatin
		Netupitant 100mg + Palonosetron 0.5mg po	135/135			
		Netupitant 200mg + Palonosetron 0.5mg po	138/137			
		Netupitant 300mg + Palonosetron 0.5mg po	136/135			
		Aprepitant regimen[a] po + Ondansetron 32mg IV	134/134 (679/677)			
NETU-08-18	Randomized (1:1), double-blind, parallel, active-controlled	Netupitant 300mg/ Palonosetron 0.5mg po	725/724	Initial and Multiple cycle	28 M 1422 F 54.0 (22-79)	anthracycline and cyclophosphamide
		Palonosetron 0.50mg po	725/725 (1450/1449)			

a. Aprepitant regimen = 125 mg on day 1, 80 mg on days 2 and 3

Study NETU-07-07

In a multicenter, randomized, parallel, double-blind, controlled clinical trial of 679 treated patients, the efficacy and safety of a single dose of oral netupitant in combination with oral palonosetron was compared with a single oral dose of palonosetron in cancer patients receiving the first cycle of a chemotherapy regimen that included cisplatin (median dose=75 mg/m^2). All patients also received a dexamethasone regimen. The efficacy of **Akynzeo** was assessed in 135 patients who received **Akynzeo** (netupitant 300 mg and palonosetron 0.5 mg) and 136 patients who received oral palonosetron 0.5 mg.

Treatment regimens for the **Akynzeo** and palonosetron arms are summarized in Table 7.

Table 7: Oral Antiemetic Treatment Regimen in Study NETU-07-07

Treatment Regimen	Day 1	Days 2 to 4
Akynzeo	**Akynzeo** 300 mg netupitant/0.5 mg palonosetron 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 the Complete Response (CR) rate (defined as no emetic episodes, no rescue medication) within 120 hours after the start of the highly emetogenic chemotherapy administration.

A summary of the key results from this study is shown in Table 8.

Table 8: Proportion of Patients Responding by Treatment Group and Phase in Study NETU-07-07

ENDPOINTS	**Akynzeo 300 mg netupitant/0.5 mg palonosetron (N= 135) %**	**Palonosetron 0.5 mg (N=136) %**	**p-value[d]**
PRIMARY ENDPOINT			
Complete Response			
Overall[a]	89.6	76.5	0.004
KEY SECONDARY ENDPOINTS			
Complete Response			
Acute Phase[b]	98.5	89.7	0.007
Delayed Phase[c]	90.4	80.1	0.018
No Emesis			
Overall	91.1	76.5	0.001
Acute Phase	98.5	89.7	0.007
Delayed Phase	91.9	80.1	0.006
No Significant Nausea			
Overall	89.6	79.4	0.021

Table 8: Proportion of Patients Responding by Treatment Group and Phase in Study NETU-07-07

ENDPOINTS	**Akynzeo 300 mg netupitant/0.5 mg palonosetron (N= 135) %**	**Palonosetron 0.5 mg (N=136) %**	**p-value[d]**
Acute Phase	98.5	93.4	0.050
Delayed Phase	90.4	80.9	0.027

a. Overall: 0 to 120 hours post-chemotherapy regimen.
b. Acute phase: 0 to 24 hours post-chemotherapy regimen.
c. Delayed phase: 25 to 120 hours post-chemotherapy regimen.
d. Adjusted p-values for multiple comparisons using Cochran-Mantel-Haenszel test, stratified by gender.

Study NETU-08-18

In a multicenter, randomized, parallel, double-blind, active controlled, superiority trial, 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 (AC) 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.

Treatment regimens for the **Akynzeo** and palonosetron arms are summarized in Table 9.

Table 9: Oral Antiemetic Treatment Regimen in Study NETU-08-18

Treatment Regimen	**Day 1**	**Days 2 to 3**
Akynzeo	**Akynzeo** 300 mg netupitant / 0.5 mg palonosetron 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 1455 patients were randomized to the **Akynzeo** arm or palonosetron arm. A total of 1450 patients (**Akynzeo**, n=724; 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, with 5 (0.3%) patients completing eight treatment cycles.

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

A summary of the key results from this study is shown in Table 10.

Table 10: Proportion of Patients Responding by Treatment Group and Phase – Cycle 1 in Study NETU-08-18

ENDPOINTS	**Akynzeo 300 mg netupitant/0.5 mg palonosetron (N= 724) %**	**Palonosetron 0.5 mg (N=725) %**	**p-value[d]**
PRIMARY ENDPOINT			
Complete Response			
Delayed Phase[a]	76.9	69.5	0.001
KEY SECONDARY ENDPOINTS			
Complete Response			
Acute Phase[b]	88.4	85.0	0.047
Overall[c]	74.3	66.6	0.001
No Emesis			
Overall	79.8	72.1	<0.001
Acute Phase	90.9	87.3	0.025
Delayed Phase	81.8	75.6	0.004
No Significant Nausea			
Overall	74.6	69.1	0.020
Acute Phase	87.3	87.9	NS
Delayed Phase	76.9	71.3	0.014

a. Delayed phase: 25 to 120 hours after chemotherapy regimen.
b. Acute phase: 0 to 24 hours after chemotherapy regimen.
c. Overall: 0 to 120 hours after chemotherapy regimen.
d. p-value from Cochran-Mantel-Haenszel test, stratified by class and region.
NS=Not Statistically Significant

Multiple Cycles

Study NETU-08-18 patients continued into the Multiple-Cycle extension for up to 7 additional cycles of chemotherapy. Only a limited number of patients, however, received treatment beyond cycle 6. During all cycles, the CR rate in the delayed phase was higher for **Akynzeo** than for palonosetron. Antiemetic activity of **Akynzeo** was maintained throughout repeat cycles for those patients continuing in each of the multiple cycles.

DETAILED PHARMACOLOGY

Netupitant

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 substances produce nausea and

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

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

Netupitant was shown to cross the blood brain barrier with a NK_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.

Netupitant and its metabolites, M1, M2, and M3, caused concentration-dependent suppression of hERG potassium currents in CHO cells stably transfected with hERG cDNA, with IC50 values as follows, based on actual concentrations: netupitant 439.7 ng/mL, M1 474.3 ng/mL, M2 25,568.2 ng/mL, and M3 2,616.3 ng/mL.

Palonosetron

Palonosetron is a potent and effective 5-HT_3 receptor antagonist and its antiemetic actions have been clearly demonstrated in a variety of *in vivo* studies. It has no clinically significant action on other serotonergic receptors.

Although most *in vivo* studies were limited to intravenous dosages of up to 1 mg/kg, this is 300-fold higher than the proposed human dose. Day 1 toxicokinetics in dogs treated intravenously at this dosage suggest that the C_{max} was about 65•fold higher than the maximum expected human exposure. Exposures in the oral rat studies were probably sub-therapeutic.

In comparison to palonosetron, the two main metabolites found in humans (M9 and M4) demonstrated at least a 100-fold lower antagonistic activity at the 5-HT_3 receptor in an *in vitro* model of isolated guinea pig ileum. In addition, they were detected only in low or trace amounts in patients receiving palonosetron. The marginal 5-HT_3 antagonist activity of M4 and M9 is considered clinically non relevant.

The pattern of major metabolites in rats, dogs and primates differed from each other and from humans. The plasma kinetics in monkeys are closer to those of dogs than humans. Palonosetron, but none of its metabolites, passes the blood-brain barrier in rats and was rapidly cleared from the brain, suggesting that it reaches the intended site of action and does not accumulate. Excretion was primarily urinary in all species including humans. There was evidence of reversible melanin binding of palonosetron or one of its metabolites in pigmented rats. No treatment-related ocular changes have been seen.
In HEK293 cells stably transfected with hERG cDNA, palonosetron caused a concentration-dependent suppression of hERG currents, with an IC50 values of 679.1 ng/mL, based on nominal concentrations.

In HEK293 cells stably transfected with cDNA for the hHNa sodium channel, palonosetron caused a concentration-dependent suppression of the hHNa sodium current, with an IC50 value of 2,164

ng/mL, based on nominal concentrations.

TOXICOLOGY

Single-Dose Toxicity

Netupitant

A single oral dose was lethal in mice at ≥1000 and in rats at 2000 mg/kg. Lethality occurred approximately 1 week after the dosing. Generalized clinical signs were noted, as well as body weight loss. Microscopic changes consistent with phospholipidosis were noted in multiple tissues at ≥1000 mg/kg and were associated with necrosis in some tissues at ≥1000 mg/kg in mice and at ≥1500 mg/kg in rats. A single oral dose of 200, 300, or 400 mg/kg in dogs resulted in vomiting, liquid feces, and/or subdued behavior and reduced body weight gain/body weight loss at all doses. There were microscopic changes consistent with phospholipidosis in the gall bladder at 400 mg/kg.

Palonosetron

Single oral doses of 500 mg/kg and 100 mg/kg were lethal in rats and dogs, respectively. Death was preceded by severe clinical signs including convulsions. Oral dosing resulted in ataxia, inactivity, and tremors at 250 mg/kg in rats and emesis and inactivity at 50 mg/kg in dogs.

Repeat-Dose Toxicity

Netupitant

Repeat dose toxicity was characterized in rats, dogs, and mice. Effects on body weights were noted and body weight loss was dose limiting in all three species. Similarly, histopathological findings consistent with phospholipidosis also occurred in rats, dogs, and mice. The doses at which phospholipidosis was noted decreased with repeated dosing and exposures (AUCs) at the NOAELs in studies at or exceeding 4 weeks ranged from twice to below the 14,400 ng·h/mL in humans at the recommended therapeutic dose of 300 mg. However, it is noteworthy that while phospholipidosis was induced after a single dose in rats and dogs, it was only at very high doses, which are not relevant to the single dose clinical dosing regimen. Thus, while there are no or very low margins of safety at the NOAELs after repeated dosing with respect to phospholipidosis, it is not a significant concern after a single dose of 300 mg netupitant in cancer patients.

In conscious telemetry dogs (N=6/group) receiving negative control, vehicle, palonosetron 10 mg/kg/netupitant 2 mg/kg, palonosetron 10 mg/kg/netupitant 10 mg/kg, and palonosetron 10 mg/kg/ netupitant 50 mg/kg for 15 days by oral gavage, dose-dependent prolongation of the QTc, QRS, and PR intervals was observed.

Palonosetron

Chronic intravenous administration to rats and oral treatment to mice at sub-lethal dosages was essentially without any evidence of toxicity. Treatment of dogs at marginally sublethal dosages, whether given orally or intravenously, was associated with convulsions, some other signs and, following oral treatment, a few minor clinical pathology changes, of which reduced alkaline phosphatase activity and increased cholesterol concentrations extended to lower dosages. There were no consistent anatomic pathology changes in dogs or mice, or in rats when treated intravenously. All of these studies were associated with high exposures to palonosetron.

In dogs, deaths were clearly associated with severe clinical signs, including convulsions, and the signs were generally associated with dosing and short-lived with rapid recovery.

Netupitant and its Combination with Palonosetron
Repeated oral dosing for up to 13 weeks with combinations of palonosetron and netupitant at doses that bracketed levels resulting in no adverse effects to those causing signs of toxicity were conducted in rats and dogs. There were no effects on toxicity that could not be attributed to either palonosetron or netupitant administered as a single agent. Administration of the combinations had no effects on C_{max} and AUC of palonosetron or netupitant.

Reproductive Toxicity
Netupitant
Daily oral administration of netupitant in rats at doses up to 30 mg/kg (1.9 times the human AUC in male rats and 3.7 times the human AUC in female rats at the recommended human dose) had no effects on fertility or reproductive performance.

Daily netupitant administration at doses up to 30 mg/kg in rats (3.7 times the human AUC at the recommended single human dose to be given with each cycle of chemotherapy) during the period of organogenesis produced no effects on embryo-fetal development. However, an increased incidence of external and skeletal abnormalities was observed in rabbit fetuses following daily administration of netupitant to rabbits at 10 mg/kg/day and higher (0.2 times the human AUC at the recommended single human dose to be given with each cycle of chemotherapy) during the period of organogenesis. These abnormalities included positional abnormalities in the limbs and paws, and fused sternebrae. Reduction in fetal rabbit weight occurred at 30 mg/kg/day. Maternal toxicity in rabbits (i.e., loss of bodyweight during the treatment period) was also observed at 30 mg/kg/day.

Daily administration of netupitant to rats during organaogenesis through lactation at doses resulting in exposures up to 3.7 times the human AUC at the recommended human dose produced no adverse effects in the offspring.

Palonosetron
There was evidence that oral treatment with palonosetron at 120 mg/kg/day reduced fertility in male rats; this dosage is associated with histopathological changes in the seminiferous epithelium. Palonosetron at oral doses up to 60 mg/kg/day (about 921 times the recommended human oral dose based on body surface area) had no effect on fertility and reproductive performance of male and female rats.
Evidence of fetal toxicity was limited to low fetal weights in rats treated at 60 or 120 mg/kg/day during organogenesis, with an associated reduction in ossification. There was no similar effect in rabbits. In a pre- and post-natal study, there was evidence of maternal toxicity at 60 mg/kg/day. Postural changes in the F1 generation were probably a consequence of this toxicity. There was no effect on development or reproduction in the F1 generation. Juvenile toxicity studies did not show any evidence of toxicity that was not apparent in adult animals.

The no-observed-adverse-effect levels in each case were similar to or greater than those observed

in repeat dose toxicity testing, suggesting that these changes only occur at exposures that significantly exceed those anticipated during clinical use.

Genotoxicity

Netupitant

Netupitant was tested for genotoxicity in the standard battery of tests that included two in vitro reverse mutation tests in bacteria (Ames test), the mouse lymphoma test (ML/TK), and an in vivo mouse micronucleus test. There was no evidence for mutagenicity or clastogenicity under the conditions of study and with and without metabolic activation in the in vitro assays.

Palonosetron

The weight of evidence indicates that palonosetron lacks genotoxic activity. In the Salmonella (Ames) reverse mutation test, there was no evidence for mutagenic activity. There was also no evidence for mutagenic activity of palonosetron in the CHO/HGPRT forward mutation assay. An *in vitro* chromosome aberration assay was conducted in CHO cells in which a clastogenic effect was observed in the absence of metabolic activation and an equivocal response with metabolic activation. An additional *in vitro* photo-chromosome aberration assay performed in V79 cells, was negative. In an *in vivo* micronucleus test in mice treated intravenously at up to 10 mg/kg, there was no evidence for mutagenic or clastogenic effects. Palonosetron was also tested in the *in vivo* Unscheduled DNA Synthesis test in rat hepatocytes at intravenous doses of up to 30mg/kg and there was no evidence for DNA damage. Overall, palonosetron is considered non-mutagenic.

Carcinogenicity

Netupitant

Long-term studies in animals to evaluate carcinogenic potential have not been performed with netupitant. In the chronic toxicity performed with netupitant (6-month in rats and 9-month in dogs) there was no evidence of preneoplastic lesions.

Palonosetron

Two carcinogenicity studies in the mouse and rat were performed. Systemic exposure to palonosetron in these studies was not linear and increased with duration of dosing.

In the mouse study there were no treatment related increases in tumour incidence in animals treated at 10, 30, or 60 mg/kg/day. The highest tested dose produced a systemic exposure to palonosetron (AUC) of about 90 to 173 times the human exposure at the recommended oral dose of 0.5 mg.

In the rat study, there were statistically significant increased incidences of a variety of tumours affecting the adrenal, liver, mammary gland, pancreas, pituitary, skin, tail and thyroid. These tumours occurred at high doses (15, 30 and 60 mg/kg/day) administered for 2 years. The highest doses produced a systemic exposure to palonosetron (AUC) of 82 and 185 times the human exposure at the recommended dose. Although the underlying mechanism of palonosetron tumorigenicity is not known, it may be associated with disruption of neuroendocrine pathways.

REFERENCES

1. Aapro M, Rugo H, Rossi G, Rizzi G, Borroni ME, Bondarenko I, et al. A randomized Phase 3 study evaluating the efficacy and safety of NEPA, a fixed-dose combination of netupitant and palonosetron, for prevention of chemotherapy-induced nausea and vomiting following moderately emetogenic chemotherapy. Ann Oncol 2014;25:1328–1333.

2. Gralla R, Bosnjak SM, Hontsa A, Balser C, Rizzi G, Rossi G, et al. A Phase 3 study evaluating the safety and efficacy of NEPA, a fixed-dose combination of netupitant and palonosetron, for prevention of chemotherapy-induced nausea and vomiting over repeated cycles of chemotherapy. Ann Oncol 2014;25:1333–1339.

3. Hesketh PJ, Rossi G, Rizzi G, Palmas M, Alyasova A, Bondarenko I, Lisyanskaya A, Gralla R. Efficacy and safety of NEPA, an oral combination of netupitant and palonosetron, for prevention of chemotherapy-induced nausea and vomiting following highly emetogenic chemotherapy: A randomized dose-ranging pivotal study. Ann Oncol 2014;25:1340-6.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

[Pr]Akynzeo®
netupitant / palonosetron capsules

Read this carefully before you start taking **Akynzeo** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Akynzeo**.

Serious Warnings and Precautions

Akynzeo can interact with certain medications that are broken down by similar liver enzymes. Tell your doctor which medications you are taking.

What is Akynzeo used for?
Prevention of nausea (feeling sick) and vomiting that may happen after taking certain anti-cancer medicines (chemotherapy). You will take **Akynzeo** with another medication called dexamethasone.

Akynzeo can help prevent nausea and vomiting during two different phases:
- Acute phase: within 24 hours of chemotherapy
- Delayed phase: ongoing nausea and vomiting for 5 days after chemotherapy

How does Akynzeo work?
Akynzeo is a type of medication called an "anti-emetic." It contains a combination of palonosetron and netupitant:
- palonosetron prevents nausea and vomiting during the acute phase
- netupitant prevents nausea and vomiting during the delayed phase after cancer chemotherapy.

What are the ingredients in Akynzeo?
Medicinal ingredients: netupitant and palonosetron (as palonosetron hydrochloride).

Non-medicinal ingredients: glycerol monocaprylocaprate,microcrystalline cellulose, sucrose lauric acid esters, povidone K-30, croscarmellose sodium, colloidal hydrated silica, sodium stearyl fumarate, magnesium stearate, glycerin, polyglyceryl dioleate, purified water, butylated hydroxyanisole (BHA), gelatin, sorbitol, 1,4 sorbitan, titanium dioxide, shellac glaze (partially esterified), yellow, red and black iron oxide, propylene glycol. May contain traces of lecithin derived from soya, medium-chain triglycerides, and denatured ethanol.

Akynzeo comes in the following dosage form:
Capsule: 300 mg netupitant / 0.5 mg palonosetron (as palonosetron hydrochloride)

Do not use Akynzeo if:

- you are allergic to netupitant or palonosetron or any of the other ingredients in **Akynzeo**;
- you are pregnant or planning to become pregnant during therapy and up to one month after treatment with **Akynzeo**;
- you take pimozide, terfenadine, astemizole, or cisapride. Taking **Akynzeo** with these medications could result in serious or life-threatening problems.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Akynzeo. Talk about any health conditions or problems you may have, including if you:

- have any heart disorder, including an irregular heartbeat, prolongation of the QT interval or a family history of QT prolongation or sudden cardiac death at less than 50 years of age;
- have low levels of potassium or magnesium;
- have high blood pressure;
- have liver or kidney problems;
- have acute bowel blockage or a history of repeated constipation;
- are allergic to other 5-HT_3 receptor antagonists such as ondansetron, dolasetron, or granisetron;
- are allergic to sorbitol or sucrose. If you do, you should not take **Akynzeo**.

Other warnings you should know about:
Akynzeo may cause a severe allergic reaction. Symptoms include swelling of the face, lips or tongue, difficulty breathing, rash, or fainting.

Do not take **Akynzeo** if you are less than 18 years old.

Driving and using machines:
Akynzeo may influence your ability to drive and use machines. Do not drive or use machines until you know how you feel while taking **Akynzeo**. It may cause dizziness, drowsiness or may make you feel tired.

Soya Allergy:
Akynzeo may contain a trace of lecithin derived from soya. If you have a peanut or soya allergy you may be monitored for signs of an allergic reaction.

Pregnancy:
Do not take **Akynzeo** if you are pregnant or are planning to get pregnant. Your doctor may ask you to take a pregnancy test before you start treatment with **Akynzeo**. You must use effective birth control (such as 'the pill') during treatment with **Akynzeo** and up to one month after treatment.

Nursing Women:
Do not use **Akynzeo** if you are breast-feeding and for 1 month after your last dose.

Serotonin Syndrome:
Serotonin Syndrome is a rare but potentially life-threatening reaction that can occur with "antiemetic" medicines. It can cause serious changes in how your brain, muscles and digestive system work. Serotonin Syndrome symptoms include:

- fever, sweating, shivering, diarrhea, nausea, vomiting;
- muscle shakes, jerks, twitches or stiffness, overactive reflexes, loss of coordination;
- fast heartbeat, changes in blood pressure;
- confusion, agitation, restlessness, hallucinations, mood changes, unconsciousness, and coma.

The reaction is more likely to occur if you also take certain other medications. Be sure to tell your healthcare professional all the medicines you are taking.

The following may interact with Akynzeo:

- pimozide (an antipsychotic)
- terfenadine, astemizole (allergy medications)
- cisapride (used to treat reflux)
- chemotherapeutic agents such as docetaxel, etoposide, cyclophosphamide
- serotonergic drugs (including SSRIs, SNRIs) used to treat depression and/or anxiety disorders. These may increase the risk of Serotonin Syndrome.
- digoxin (used to treat certain heart conditions)
- zidovudine, ritonavir (used to treat HIV/AIDS)
- rifampin (antibiotics)
- ketoconazole (an antifungal)
- valproic acid (used to treat epilepsy)
- morphine (for pain)
- drugs that may lengthen the QT-interval of your heart (examples include certain drugs to treat heart conditions, psychosis, depression, pain, infections and other conditions)
- drugs that may affect the levels of electrolytes in your body (examples include certain diuretics, laxatives, enemas and corticosteroids)
- grapefruit and grapefruit juice

How to take Akynzeo:

- Take one **Akynzeo** capsule about 1 hour before the start of your chemotherapy cycle.
- Do not use **Akynzeo** to treat nausea or vomiting in the days after your chemotherapy. Only take it when you are one hour from a chemotherapy cycle, or as prescribed by your doctor.
- You will be given a specific amount of dexamethasone to take at specific times. This will depend on the type of chemotherapy you are taking.
- **Akynzeo** should be swallowed whole. It can be taken with or without food.
- Do not change your dose without consulting your doctor.

Refilling your Prescription for Akynzeo:

A prescription is required from your doctor each time you need more **Akynzeo**. It is important that you contact your doctor before your current supply runs out.

Overdose:

If you think you have taken too much **Akynzeo**, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

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

What are possible side effects from using Akynzeo?

These are not all the possible side effects you may feel when taking **Akynzeo**. If you experience any side effects not listed here, contact your healthcare professional.

Common side effects may include:

- headache
- constipation
- fatigue (feeling tired)

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY RARE **Severe allergic reaction (anaphylaxis):** hives, skin rash, itching, difficulty breathing or swallowing, swollen mouth, face, lips, tongue or throat and sometimes a drop in blood pressure			√
Serotonin Syndrome: fever, sweating, shivering, diarrhea, nausea, vomiting; muscle shakes, jerks, twitches or stiffness, overactive reflexes, loss of coordination; fast heartbeat, changes in blood pressure; confusion, agitation, restlessness, hallucinations, mood changes, unconsciousness, and coma.			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.
3 ways to report:

- Online at MedEffect (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 1908C
    Ottawa, ON
    K1A 0K9

    Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store at 15-30°C.
- Keep out of the reach and sight of children.

If you want more information about Akynzeo:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp); the manufacturer's website http://www.gud-knight.com, or by calling 844-483-5636.

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