PRODUCT MONOGRAPH

**Pr**<sup>™</sup> Akynzeo

(netupitant/palonosetron)
capsules

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

Antiemetic
(NK<sub>1</sub> receptor antagonist/5-HT<sub>3</sub> receptor antagonist)

A04AA55

Purdue Pharma
575 Granite Court
Pickering, Ontario
L1W 3W8

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Dosage Form / Strength</th>
<th>Non-medicinal Ingredients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>Capsule: 300 mg / 0.5 mg netupitant / palonosetron (as palonosetron hydrochloride)</td>
<td>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.</td>
</tr>
</tbody>
</table>

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-HT₃ 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

<table>
<thead>
<tr>
<th>Serious Warnings and Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug interactions may occur with medicinal products, including chemotherapeutic agents (see WARNINGS AND PRECAUTIONS) that are metabolized through CYP3A4 (see DRUG INTERACTIONS).</td>
</tr>
</tbody>
</table>

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-HT3 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-HT3 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>
<thead>
<tr>
<th>System Organ Class</th>
<th>Preferred Term</th>
<th>netupitant 300 mg / palonosetron 0.5 mg (n=136) n (%)</th>
<th>palonosetron 0.5 mg (n=136) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and Lymphatic System Disorders</td>
<td>Leukocytosis</td>
<td>5 (3.7)</td>
<td>10 (7.4)</td>
</tr>
<tr>
<td></td>
<td>Lymphocytosis</td>
<td>3 (2.2)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td></td>
<td>Neutrophilia</td>
<td>5 (3.7)</td>
<td>4 (2.9)</td>
</tr>
<tr>
<td>Cardiac Disorders</td>
<td>Bundle branch block</td>
<td>3 (2.2)</td>
<td>-</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>Abdominal pain upper</td>
<td>3 (2.2)</td>
<td>2 (1.5)</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>4 (2.9)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td></td>
<td>Dyspepsia</td>
<td>6 (4.4)</td>
<td>2 (1.5)</td>
</tr>
<tr>
<td>General Disorders</td>
<td>Asthenia</td>
<td>12 (8.8)</td>
<td>13 (9.6)</td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
<td>6 (4.4)</td>
<td>3 (2.2)</td>
</tr>
</tbody>
</table>
Table 1: Treatment Emergent Adverse Events Occurring in ≥ 2% of Cancer Patients Receiving Akynzeo and Cisplatin Based Highly Emetogenic Chemotherapy (Cycle 1) (Study NETU-07-07)

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Preferred Term</th>
<th>netupitant 300 mg / palonosetron 0.5 mg (n=136) n (%)</th>
<th>palonosetron 0.5 mg (n=136) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Investigations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Alanine aminotransferase increased</td>
<td>9 (6.6)</td>
<td>9 (6.6)</td>
</tr>
<tr>
<td></td>
<td>Aspartate aminotransferase increased</td>
<td>6 (4.4)</td>
<td>5 (3.7)</td>
</tr>
<tr>
<td></td>
<td>Blood urea increased</td>
<td>3 (2.2)</td>
<td>9 (6.6)</td>
</tr>
<tr>
<td><strong>Metabolism and Nutrition Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anorexia</td>
<td>5 (3.7)</td>
<td>11 (8.1)</td>
</tr>
<tr>
<td><strong>Nervous System Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>5 (3.7)</td>
<td>9 (6.6)</td>
</tr>
<tr>
<td><strong>Respiratory Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hiccups</td>
<td>7 (5.1)</td>
<td>7 (5.1)</td>
</tr>
<tr>
<td><strong>Skin and Subcutaneous Tissue Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Erythema</td>
<td>4 (2.9)</td>
<td>2 (1.5)</td>
</tr>
<tr>
<td><strong>Vascular disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
<td>3 (2.2)</td>
<td>1 (0.7)</td>
</tr>
</tbody>
</table>

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% of Cancer Patients Receiving Akynzeo and Anthracyclines and Cyclophosphamide Based Chemotherapy (Cycle 1) (Study NETU-08-18)

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Preferred Term</th>
<th>netupitant 300 mg / palonosetron 0.5mg (n=725) n (%)</th>
<th>palonosetron 0.5mg (n=725) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood and Lymphatic System Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anemia</td>
<td>26 (3.6)</td>
<td>24 (3.3)</td>
</tr>
<tr>
<td></td>
<td>Leukopenia</td>
<td>96 (13.2)</td>
<td>90 (12.4)</td>
</tr>
<tr>
<td></td>
<td>Lymphopenia</td>
<td>21 (2.9)</td>
<td>14 (1.9)</td>
</tr>
<tr>
<td></td>
<td>Neutropenia</td>
<td>173 (23.9)</td>
<td>182 (25.1)</td>
</tr>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>31 (4.3)</td>
<td>26 (3.6)</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>22 (3.0)</td>
<td>27 (3.7)</td>
</tr>
<tr>
<td></td>
<td>Stomatitis</td>
<td>17 (2.3)</td>
<td>9 (1.2)</td>
</tr>
</tbody>
</table>
Table 2: Treatment Emergent Adverse Events Occurring in ≥ 2% of Cancer Patients Receiving Akynzeo and Anthracyclines and Cyclophosphamide Based Chemotherapy (Cycle 1) (Study NETU-08-18)

<table>
<thead>
<tr>
<th>System Organ Class Preferred Term</th>
<th>netupitant 300 mg / palonosetron 0.5mg (n=725) n (%)</th>
<th>palonosetron 0.5mg (n=725) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthenia</td>
<td>59 (8.1)</td>
<td>50 (6.9)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>47 (6.5)</td>
<td>38 (5.2)</td>
</tr>
<tr>
<td><strong>Metabolism and Nutrition Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>25 (3.4)</td>
<td>32 (4.4)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>24 (3.3)</td>
<td>25 (3.4)</td>
</tr>
<tr>
<td><strong>Nervous System Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>15 (2.1)</td>
<td>11 (1.5)</td>
</tr>
<tr>
<td>Headache</td>
<td>64 (8.8)</td>
<td>52 (7.2)</td>
</tr>
<tr>
<td><strong>Skin and Subcutaneous Tissue Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>253 (34.9)</td>
<td>253 (34.9)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Laboratory Changes</th>
<th>netupitant 300mg / palonosetron 0.5mg (n = 861)</th>
<th>palonosetron 0.5mg (n = 861)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST &gt; 3 x ULN and/or ALT &gt; 3 x ULN with Total Bilirubin &gt; ULN</td>
<td>3 (0.3%)</td>
<td>5 (0.6%)</td>
</tr>
<tr>
<td>AST &gt; 10 x ULN and/or ALT &gt; 10 x ULN with Total Bilirubin &gt; ULN</td>
<td>-</td>
<td>2 (0.2%)</td>
</tr>
<tr>
<td>AST &gt; 3 x ULN and/or ALT &gt; 3 x ULN with Total Bilirubin ≥ 2 x ULN</td>
<td>1 (0.1%)</td>
<td>1 (0.1%)</td>
</tr>
</tbody>
</table>

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-HT3 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

<table>
<thead>
<tr>
<th>Drug/Drug Class</th>
<th>Ref</th>
<th>Effect</th>
<th>Clinical Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pimozide</td>
<td>T</td>
<td>Increased pimozide concentration</td>
<td>Potentially causing serious or life-threatening reactions.</td>
</tr>
<tr>
<td>Terfenadine</td>
<td>T</td>
<td>Increased terfenadine concentration</td>
<td>Potentially causing serious or life-threatening reactions.</td>
</tr>
<tr>
<td>Astemizole</td>
<td>T</td>
<td>Increased astemizole concentration</td>
<td>Potentially causing serious or life-threatening reactions.</td>
</tr>
<tr>
<td>Cisapride</td>
<td>T</td>
<td>Increased cisapride concentration</td>
<td>Potentially causing serious or life-threatening reactions.</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>CT</td>
<td>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.</td>
<td>50% reduction of dexamethasone dose recommended</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>CT</td>
<td>Co-administration with <strong>Akynzeo</strong> caused a 35% increase in docetaxel AUC.</td>
<td>Caution and monitoring for adverse reactions in patients receiving chemotherapeutic agents metabolized by CYP3A4.</td>
</tr>
<tr>
<td>Etoposide</td>
<td>CT</td>
<td>Co-administration with <strong>Akynzeo</strong> caused a 28% increase in etoposide AUC.</td>
<td>Caution and monitoring for adverse reactions in patients receiving chemotherapeutic agents metabolized by CYP3A4.</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>CT</td>
<td>Co-administration with netupitant showed no consistent effect.</td>
<td>Caution and monitoring for adverse reactions in patients receiving chemotherapeutic agents metabolized by CYP3A4.</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>CT</td>
<td>Co-administration of netupitant caused a 1.3-fold increase in erythromycin AUC. Netupitant pharmacokinetics unaffected.</td>
<td>Not considered clinically significant.</td>
</tr>
<tr>
<td>Midazolam</td>
<td>CT</td>
<td>Co-administration of netupitant caused a 2.4-fold increase in midazolam AUC. Netupitant pharmacokinetics unaffected.</td>
<td>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.</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>CT</td>
<td>Co-administration with <strong>Akynzeo</strong></td>
<td>Clinically relevant effects on</td>
</tr>
</tbody>
</table>
Table 4: Established or Potential Drug-Drug Interactions with Akynzeo

<table>
<thead>
<tr>
<th>Drug/Drug Class</th>
<th>Ref</th>
<th>Effect</th>
<th>Clinical Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>(ethinylestradiol, levonorgestrel)</td>
<td></td>
<td>caused a 1.4-fold increase in levonorgestrel AUC.</td>
<td>hormonal contraception unlikely.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No significant effect on ethinylestradiol.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Netupitant and palonosetron pharmacokinetics unaffected.</td>
<td></td>
</tr>
<tr>
<td>CYP3A4 Inducers (e.g. rifampin)</td>
<td>CT</td>
<td>Presence of rifampin caused a 5.2-fold decrease in netupitant AUC. Palonosetron pharmacokinetics unaffected.</td>
<td>Concomitant use of Akynzeo should be avoided in patients using strong CYP3A4 inducers.</td>
</tr>
<tr>
<td>CYP3A4 Inhibitors (e.g. ketoconazole)</td>
<td>CT</td>
<td>Presence of ketoconazole caused a 1.8-fold increase in netupitant AUC. No effect on palonosetron.</td>
<td>Caution is recommended if Akynzeo is coadministered with strong CYP3A4 inhibitors.</td>
</tr>
<tr>
<td>P-gp Substrates (e.g. digoxin)</td>
<td>CT</td>
<td>In vitro data shows that netupitant is a P-gp inhibitor. Netupitant did not affect the AUC of digoxin but increased the C\text{\textsubscript{max}} by 1.09-fold.</td>
<td>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.</td>
</tr>
<tr>
<td>Serotonergic Drugs</td>
<td>C\textsuperscript{a}</td>
<td>Reports of serotonin syndrome with concomitant use of 5-HT\textsubscript{3} antagonists and other serotonergic drug products (including SSRIs and SNRIs).</td>
<td>Caution recommended if Akynzeo combined with other serotonergic drug products.</td>
</tr>
<tr>
<td>UGT2B7 Substrates (e.g. zidovudine, valproic acid, morphine)</td>
<td>IV</td>
<td>In vitro data indicates that netupitant inhibits UGT2B7.</td>
<td>Clinical relevance is unknown. Caution recommended if Akynzeo is combined with an oral substrate of this enzyme.</td>
</tr>
</tbody>
</table>

\textsuperscript{a} CT = Clinical Trial  
\textsuperscript{b} C = Case Study  
\textsuperscript{c} T = Theoretical  
\textsuperscript{d} IV = In Vitro

\textit{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 PHARMACOLOGY, 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-HT3 and NK1 receptor neuropathways.

Netupitant is a selective antagonist of human substance P/neurokinin 1 (NK1) receptors. Delayed emesis has been associated with the activation of tachykinin family neurokinin 1 (NK1) 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-HT3 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>
<thead>
<tr>
<th>Table 5: PK Parameters (mean and CV%) After Single Dose Administration of Akynzeo in Healthy Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>C(_{\text{max}}) (ng/mL)</td>
</tr>
<tr>
<td>T(_{\text{max}}) (h)</td>
</tr>
<tr>
<td>AUC (ng h/mL)</td>
</tr>
<tr>
<td>T(_{1/2}) (h)</td>
</tr>
</tbody>
</table>

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\(_{\text{max}}\) and AUC of netupitant and its metabolites were similar to those in healthy subjects. The mean C\(_{\text{max}}\) 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\(_{\text{max}}\) in approximately 5 hours. There was a greater than dose proportional increase in C\(_{\text{max}}\) and AUC parameters with dose increases from 10 mg to 300 mg, and a dose-proportional increase in C\(_{\text{max}}\) 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\(_{\text{max}}\), a 1.02 fold increase for AUC and a 1.36 fold increase in half-life.

Netupitant AUC\(_{0-\infty}\) and C\(_{\text{max}}\) 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 ($C_{\text{max}}$) 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 ($C_{\text{max}}$) was 0.81 ± 1.66 ng/mL (mean ± SD) and time to maximum concentration ($T_{\text{max}}$) was 5.1 ± 1.7 hours. In female subjects (n=18), the mean AUC was 35% higher and the mean $C_{\text{max}}$ 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, $C_{\text{max}}$ was 0.93 ± 0.34 ng/mL and $T_{\text{max}}$ 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 $C_{\text{max}}$ 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 $C_{\text{max}}$ 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 $[^{14}\text{C}]-$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 $[^{14}\text{C}]-$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 ($t_{1/2}$) of palonosetron was 37 ± 12 hours (mean ± SD), and in cancer patients, $t_{1/2}$ 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 $C_{\text{max}}$ 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 $C_{\text{max}}$ 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 ($C_{\text{max}}$, 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 C\(_{\text{max}}\) 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\(_{\text{max}}\) 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$_{6}$N$_{4}$O

Molecular mass: 578.61 g/mol

Structural formula:

![Figure 1: Structural formula – netupitant](image)

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: (3a$\text{S}$)-2-[(S)-1-Azabicyclo [2.2.2]oct-3-yl]-2,3,3a,4,5,6-hexahydro-1-oxo-1Hbenz[de]isoquinoline hydrochloride

Molecular formula: C$_{19}$H$_{24}$N$_{2}$O$\cdot$HCl

Molecular mass: 332.87 g/mol
Structural formula:

Figure 2: Structural formula - palonosetron hydrochloride

![Structural formula](image)

**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>
<thead>
<tr>
<th>Study ID</th>
<th>Study Number</th>
<th>Design Control Type</th>
<th>Study &amp; Control Drugs</th>
<th>Number of Subjects by Arm</th>
<th>Gender M/F</th>
<th>Median Age Range (years)</th>
<th>Chemotherapy Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>NETU-07-07</td>
<td>Randomized</td>
<td>(1:1:1:1) double-blind, parallel</td>
<td>Palonosetron 0.5mg po, Netupitant 100mg + Palonosetron 0.5mg po, Netupitant 200mg + Palonosetron 0.5mg po, Netupitant 300mg + Palonosetron 0.5mg po, Aprepitant regimen + Ondansetron 32mg IV</td>
<td>136/136, 135/135, 138/137, 136/135, 134/134</td>
<td>1 cycle</td>
<td>387 M 292 F 55.0 (19-82)</td>
<td>cisplatin</td>
</tr>
<tr>
<td>NETU-08-18</td>
<td>Randomized</td>
<td>(1:1), double-blind, parallel, active-controlled</td>
<td>Netupitant 300mg/ Palonosetron 0.5mg po, Palonosetron 0.50mg po</td>
<td>725/724, 725/725 (1450/1449)</td>
<td>Initial and Multiple cycle</td>
<td>28 M 1422 F 54.0 (22-79)</td>
<td>anthracycline and cyclophosphamide</td>
</tr>
</tbody>
</table>

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/m²). 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>
<thead>
<tr>
<th>Treatment Regimen</th>
<th>Day 1</th>
<th>Days 2 to 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Akynzeo</strong></td>
<td><strong>Akynzeo 300 mg netupitant/0.5 mg palonosetron</strong>&lt;br&gt;Dexamethasone 12 mg</td>
<td>Dexamethasone 8 mg once a day</td>
</tr>
<tr>
<td><strong>Palonosetron</strong></td>
<td>Palonosetron 0.5 mg&lt;br&gt;Dexamethasone 20 mg</td>
<td>Dexamethasone 8 mg twice a day</td>
</tr>
</tbody>
</table>

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>
<thead>
<tr>
<th>ENDPOINTS</th>
<th>Akynzeo 300 mg netupitant/0.5 mg palonosetron (N=135) %</th>
<th>Palonosetron 0.5 mg (N=136) %</th>
<th>p-value&lt;sup&gt;d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRIMARY ENDPOINT</td>
<td>Complete Response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall&lt;sup&gt;a&lt;/sup&gt;</td>
<td>89.6</td>
<td>76.5</td>
<td>0.004</td>
</tr>
<tr>
<td>KEY SECONDARY ENDPOINTS</td>
<td>Complete Response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute Phase&lt;sup&gt;b&lt;/sup&gt;</td>
<td>98.5</td>
<td>89.7</td>
<td>0.007</td>
</tr>
<tr>
<td>Delayed Phase&lt;sup&gt;c&lt;/sup&gt;</td>
<td>90.4</td>
<td>80.1</td>
<td>0.018</td>
</tr>
<tr>
<td>No Emesis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>91.1</td>
<td>76.5</td>
<td>0.001</td>
</tr>
<tr>
<td>Acute Phase</td>
<td>98.5</td>
<td>89.7</td>
<td>0.007</td>
</tr>
<tr>
<td>Delayed Phase</td>
<td>91.9</td>
<td>80.1</td>
<td>0.006</td>
</tr>
</tbody>
</table>
Table 8: Proportion of Patients Responding by Treatment Group and Phase in Study NETU-07-07

<table>
<thead>
<tr>
<th>ENDPOINTS</th>
<th>Akynzeo 300 mg netupitant/0.5 mg palonosetron (N= 135) %</th>
<th>Palonosetron 0.5 mg (N=136) %</th>
<th>p-value&lt;sup&gt;d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Significant Nausea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>89.6</td>
<td>79.4</td>
<td>0.021</td>
</tr>
<tr>
<td>Acute Phase</td>
<td>98.5</td>
<td>93.4</td>
<td>0.050</td>
</tr>
<tr>
<td>Delayed Phase</td>
<td>90.4</td>
<td>80.9</td>
<td>0.027</td>
</tr>
</tbody>
</table>

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.

**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

<table>
<thead>
<tr>
<th>Treatment Regimen</th>
<th>Day 1</th>
<th>Days 2 to 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akynzeo</td>
<td>Akynzeo 300 mg netupitant / 0.5 mg palonosetron Dexamethasone 12 mg</td>
<td>No antiemetic treatment</td>
</tr>
<tr>
<td>Palonosetron</td>
<td>Palonosetron 0.5 mg Dexamethasone 20 mg</td>
<td>No antiemetic treatment</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>ENDPOINTS</th>
<th>Akynzeo 300 mg netupitant/0.5 mg palonosetron (N=724) %</th>
<th>Palonosetron 0.5 mg (N=725) %</th>
<th>p-value&lt;sup&gt;d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PRIMARY ENDPOINT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete Response</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delayed Phase&lt;sup&gt;a&lt;/sup&gt;</td>
<td>76.9</td>
<td>69.5</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>KEY SECONDARY ENDPOINTS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete Response</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute Phase&lt;sup&gt;b&lt;/sup&gt;</td>
<td>88.4</td>
<td>85.0</td>
<td>0.047</td>
</tr>
<tr>
<td>Overall&lt;sup&gt;c&lt;/sup&gt;</td>
<td>74.3</td>
<td>66.6</td>
<td>0.001</td>
</tr>
<tr>
<td>No Emesis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>79.8</td>
<td>72.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Acute Phase</td>
<td>90.9</td>
<td>87.3</td>
<td>0.025</td>
</tr>
<tr>
<td>Delayed Phase</td>
<td>81.8</td>
<td>75.6</td>
<td>0.004</td>
</tr>
<tr>
<td>No Significant Nausea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>74.6</td>
<td>69.1</td>
<td>0.020</td>
</tr>
<tr>
<td>Acute Phase</td>
<td>87.3</td>
<td>87.9</td>
<td>NS</td>
</tr>
<tr>
<td>Delayed Phase</td>
<td>76.9</td>
<td>71.3</td>
<td>0.014</td>
</tr>
</tbody>
</table>

<sup>a</sup> Delayed phase: 25 to 120 hours after chemotherapy regimen.  
<sup>b</sup> Acute phase: 0 to 24 hours after chemotherapy regimen.  
<sup>c</sup> Overall: 0 to 120 hours after chemotherapy regimen.  
<sup>d</sup> 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 (NK₁) receptors. Palonosetron is a 5-HT₃ 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.

Delayed emesis has been associated with the activation of tachykinin family neurokinin 1 (NK₁) 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 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.

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-HT₃ 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 Cₙₐₓ 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-HT₃ 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-HT₃ 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 Cmax 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 organogenesis 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


READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

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.

<table>
<thead>
<tr>
<th>Serious Warnings and Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akynzeo can interact with certain medications that are broken down by similar liver enzymes. Tell your doctor which medications you are taking.</td>
</tr>
</tbody>
</table>

**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 monopalmitoylrate, 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-HT₃ 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)

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

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.purdue.ca, or by calling 1-800-387-4501.

This leaflet was prepared by Purdue Pharma.

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