CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205718Orig1s000

<u>LABELING</u>

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use AKYNZEO® safely and effectively. See full prescribing information for AKYNZEO®.

AKYNZEO® (netupitant and palonosetron) capsules, for oral use
Initial U.S. Approval: 2014

----------**INDICATIONS AND USAGE**----------

AKYNZEO is a fixed combination of netupitant, a substance P/neurokinin 1 (NK_1) receptor antagonist, and palonosetron, a serotonin-3 ($5\text{-}HT_3$) receptor antagonist indicated for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy. Oral palonosetron prevents nausea and vomiting during the acute phase and netupitant prevents nausea and vomiting during both the acute and delayed phase after cancer chemotherapy. (1)

----------**DOSAGE AND ADMINISTRATION**----------

One AKYNZEO capsule administered approximately 1 hour prior to the start of chemotherapy. (2)
AKYNZEO can be taken with or without food. (2)

----------**DOSAGE FORMS AND STRENGTHS**----------

Capsule: 300 mg netupitant/0.5 mg palonosetron (3)

----------**CONTRAINDICATIONS**----------

None (4)

----------**WARNINGS AND PRECAUTIONS**----------

- Hypersensitivity reactions, including anaphylaxis, have been reported in patients receiving palonosetron with or without known hypersensitivity to other $5\text{-}HT_3$ receptor antagonists (5.1)
- Serotonin syndrome has been reported with $5\text{-}HT_3$ receptor antagonists alone but particularly with concomitant use of serotonergic drugs (5.2)

----------**ADVERSE REACTIONS**----------

Most common adverse reactions (incidence ≥3% and greater than palonosetron) are headache, asthenia, dyspepsia, fatigue, constipation and erythema (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact EISAI at 1-888-422-4743 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------**DRUG INTERACTIONS**----------

- CYP3A4 Substrates: inhibition of CYP3A4 by netupitant can result in increased plasma concentrations of the concomitant drug that can last at least 4 days and may last longer after single dosage administration of AKYNZEO; use with caution (7.1)
- CYP3A4 Inducers (e.g., rifampin): decreased plasma concentrations of netupitant; avoid use (7.2)

----------**USE IN SPECIFIC POPULATIONS**----------

- Hepatic Impairment: Avoid use in patients with severe hepatic impairment (8.6)
- Renal Impairment: Avoid use in patients with severe renal impairment or end-stage renal disease (8.7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 10/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Hypersensitivity
5.2 Serotonin Syndrome
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
7 DRUG INTERACTIONS
7.1 Effects of AKYNZEO on Other Drugs
7.2 Effects of Other Drugs on AKYNZEO
7.3 Serotonergic Drugs
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Hepatic Impairment
8.7 Renal Impairment
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

AKYNZEO is indicated for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy. AKYNZEO is an oral fixed combination of palonosetron and netupitant: palonosetron prevents nausea and vomiting during the acute phase and netupitant prevents nausea and vomiting during both the acute and delayed phase after cancer chemotherapy.

2 DOSAGE AND ADMINISTRATION

Highly Emetogenic Chemotherapy, including Cisplatin Based Chemotherapy

The recommended dosage in adults is one capsule of AKYNZEO administered approximately 1 hour prior to the start of chemotherapy with dexamethasone 12 mg administered orally 30 minutes prior to chemotherapy on day 1 and 8 mg orally once daily on days 2 to 4 *[see Clinical Studies (14),Table 5]*.

Anthracyclines and Cyclophosphamide Based Chemotherapy and Chemotherapy Not Considered Highly Emetogenic

The recommended dosage in adults is one capsule of AKYNZEO approximately 1 hour prior to the start of chemotherapy with dexamethasone 12 mg administered orally 30 minutes prior to chemotherapy on day 1. Administration of dexamethasone on days 2 to 4 is not necessary *[see Clinical Studies (14), Table 7]*.

AKYNZEO can be taken with or without food.

3 DOSAGE FORMS AND STRENGTHS

AKYNZEO (300 mg netupitant/0.5 mg palonosetron) capsules are hard gelatin capsules with white body and caramel cap with "HE1" printed on the body.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity

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

5.2 Serotonin Syndrome

The development of serotonin syndrome has been reported with 5-HT_3 receptor antagonists. Most reports have been associated with concomitant use of serotonergic drugs (e.g., selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors, mirtazapine, fentanyl, lithium, tramadol, and intravenous methylene blue). Some of the reported cases were fatal. Serotonin syndrome occurring with overdose of another 5-HT_3 receptor antagonist alone has also been reported. The majority of reports of serotonin syndrome related to 5-HT_3 receptor antagonist use occurred in a post-anesthesia care unit or an infusion center.

Symptoms associated with serotonin syndrome may include the following combination of signs and symptoms: mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, and hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, and incoordination), seizures, with or without gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Patients should be monitored for the emergence of serotonin syndrome, especially with concomitant use of AKYNZEO and other serotonergic drugs. If symptoms of serotonin syndrome occur, discontinue AKYNZEO and initiate supportive treatment. Patients should be informed of the increased risk of serotonin syndrome, especially

Reference ID: 3642902

if AKYNZEO is used concomitantly with other serotonergic drugs *[see Drug Interactions (7), Patient Counseling Information (17)]*.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The overall safety of AKYNZEO was evaluated in 1538 cancer patients and healthy volunteers in clinical trials. The data described below reflect exposure to AKYNZEO in 1169 cancer patients, receiving at least one cycle of cancer chemotherapy in 3 active-controlled trials *[see Clinical Studies (14)]*, including 782 exposed to AKYNZEO for at least 4 cycles and 321 exposed for at least 6 cycles, up to a maximum of 12 cycles of chemotherapy. The median age was 55, 79% were female, 83% were White, 13% were Asian, and 4% were Hispanic. All patients received a single oral dose of AKYNZEO 1 hour prior to the start of each chemotherapy cycle. In all studies, dexamethasone was co-administered with AKYNZEO *[see Clinical Studies (14), Table 5 and Table 7]*.

Cisplatin Based Highly Emetogenic Chemotherapy

In a single-cycle study of patients receiving cisplatin-based highly emetogenic chemotherapy, 136 patients were treated with AKYNZEO. Table 1 shows adverse reactions defined as adverse events reported at an incidence of at least 3% and for which the AKYNZEO rate exceeded palonosetron alone.

Table 1: Adverse Reactions Occurring in ≥3% of Cancer Patients Receiving AKYNZEO and Cisplatin Based Highly Emetogenic Chemotherapy (Cycle 1)

Adverse Reactions	AKYNZEO netupitant 300 mg/ palonosetron 0.5 mg (N=136)	Palonosetron 0.5 mg (N=136)
Dyspepsia	4%	2%
Fatigue	4%	2%
Constipation	3%	1%
Erythema	3%	2%

Anthracyclines and Cyclophosphamide Based Chemotherapy

In a study of patients receiving anthracycline and cyclophosphamide based chemotherapy, 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 adverse reactions defined as adverse events reported at an incidence of at least 3% and for which the AKYNZEO rate exceeded palonosetron alone during Cycle 1. The adverse reaction profile in subsequent cycles was similar to that observed in Cycle 1.

Table 2: Adverse Reactions Occurring in ≥3% of Cancer Patients Receiving AKYNZEO and Anthracyclines and Cyclophosphamide Based Chemotherapy (Cycle 1)

Adverse Reactions	AKYNZEO netupitant 300 mg/ palonosetron 0.5 mg (N=725)	Palonosetron 0.5 mg (N=725)
Headache	9%	7%
Asthenia	8%	7%
Fatigue	7%	5%

Reference ID: 3642902

In addition to the adverse reactions shown above, there were reports of concomitant elevations of transaminases > 3 x ULN and total bilirubin in both arms of the two trials that compared AKYNZEO to oral palonosetron, and the frequency of these elevations was comparable between treatment groups. See Table 3.

Table 3: Liver Function Laboratory Abnormalities

Laboratory Changes	AKYNZEO netupitant 300 mg/ palonosetron 0.5 mg N=861	Palonosetron 0.5 mg 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%)

In a multi-cycle safety study of 412 patients, the safety profile of AKYNZEO (n = 308) was comparable to aprepitant and palonosetron (n = 104) in patients undergoing initial and repeat cycles (median 5 cycles, range of 1-14 cycles) of chemotherapy, including carboplatin, cisplatin, oxaliplatin, and doxorubicin regimens. There were no reports of concomitant elevations of transaminases > 3 x ULN and total bilirubin in this study in either arm.

In a randomized, clinical non-inferiority study, that compared oral palonosetron 0.5 mg to intravenous palonosetron 0.25 mg in cancer patients scheduled to receive highly emetogenic cisplatin (≥70 mg/m^2) based chemotherapy, there were two patients (0.5%; 2/369) in the intravenous palonosetron arm who had concomitant elevations of transaminases and total bilirubin. Neither experienced transaminase elevations of > 10 x ULN.

7 DRUG INTERACTIONS

7.1 Effects of AKYNZEO on Other Drugs

Interaction with CYP3A4 Substrates

Netupitant, a component of AKYNZEO, is a moderate inhibitor of CYP3A4.

AKYNZEO should be used with caution in patients receiving concomitant medications that are primarily 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.

Dexamethasone

A two-fold increase in the systemic exposure of dexamethasone was observed 4 days after single dose of netupitant. The duration of the effect was not studied beyond 4 days. Administer a reduced dose of dexamethasone with AKYNZEO *[see Dosage and Administration (2), Clinical Pharmacology (12.3)]*.

Midazolam

When administered with netupitant, the systemic exposure to midazolam was significantly increased. Consider the potential effects of increased plasma concentrations of midazolam or other benzodiazepines metabolized via CYP3A4 (alprazolam, triazolam) when administering these drugs with AKYNZEO.

Interaction with chemotherapeutic agents

The systemic exposure of chemotherapy agents metabolized by CYP3A4 can increase when administered with AKYNZEO. Chemotherapy agents that are known to be metabolized by CYP3A4 include docetaxel,

Reference ID: 3642902

paclitaxel, etoposide, irinotecan, cyclophosphamide, ifosfamide, imatinib, vinorelbine, vinblastine, and vincristine *[see Clinical Pharmacology (12.3)]*. Caution and monitoring for chemotherapeutic related adverse reactions are advised in patients receiving chemotherapy agents metabolized primarily by CYP3A4.

Interaction with oral contraceptives

Clinically significant effect of AKYNZEO on the efficacy of oral contraceptives containing levonorgestrel and ethinyl estradiol is unlikely.

7.2 Effects of Other Drugs on AKYNZEO

Netupitant, a component of AKYNZEO, is mainly metabolized by CYP3A4 *[see Clinical Pharmacology (12.3)]*.

In vitro metabolism studies have suggested that CYP2D6 and to a lesser extent CYP3A4 and CYP1A2 are involved in the metabolism of palonosetron.

CYP3A4 Inducers

Avoid concomitant use of AKYNZEO in patients who are chronically using a strong CYP3A4 inducer such as rifampin. A strong CYP3A inducer can decrease the efficacy of AKYNZEO by substantially reducing plasma concentrations of the netupitant component *[see Clinical Pharmacology (12.3)]*.

CYP3A4 Inhibitors

Concomitant use of AKYNZEO with a strong CYP3A4 inhibitor (e.g., ketoconazole) can significantly increase the systemic exposure to the netupitant component of AKYNZEO. However, no dosage adjustment is necessary for single dose administration of AKYNZEO *[see Clinical Pharmacology (12.3)]*.

7.3 Serotonergic Drugs

Serotonin syndrome (including altered mental status, autonomic instability, and neuromuscular symptoms) has been described following the concomitant use of 5-HT_3 receptor antagonists and other serotonergic drugs, including selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs) *[see Warnings and Precautions (5.2)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Risk Summary

Adequate and well-controlled studies with AKYNZEO have not been conducted in pregnant women. In animal reproduction studies, no effects on embryo-fetal development were observed following daily administration of netupitant in pregnant rats during the period of organogenesis at doses up to 3.7 times the human AUC (area under the plasma concentration-time curve) at the recommended single human dose to be given with each cycle of chemotherapy. However, a dose-dependent increase in adverse effects on embryo-fetal development was observed following daily administration of netupitant in pregnant rabbits during the period of organogenesis with doses at least 0.2 times the human AUC at the recommended single human dose to be given with each cycle of chemotherapy. Daily administration of netupitant in rats up to 3.7 times the human AUC at the recommended human dose during organogenesis through lactation produced no adverse effects in the offspring. In animal reproduction studies with palonosetron, no effects on embryo-fetal development were observed following oral administration during the period of organogenesis at doses up to 921 and 1841 times the recommended human oral dose in rats and rabbits, respectively. AKYNZEO should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Reference ID: 3642902

Animal Data

Daily administration of up to 30 mg/kg netupitant 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 in rabbit fetuses was observed following daily administration of netupitant in 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 up to 30 mg/kg netupitant (3.7 times the human AUC at the recommended human dose) in rats during organogenesis through lactation produced no adverse effects in the offspring.

In animal reproduction studies with palonosetron, no effects on embryo-fetal development were observed in pregnant rats given oral doses up to 60 mg/kg/day (921 times the recommended human oral dose based on body surface area) or pregnant rabbits given oral doses up to 60 mg/kg/day (1841 times the recommended human oral dose based on body surface area) during the period of organogenesis.

8.3 Nursing Mothers

It is not known whether AKYNZEO is 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 Nonclinical Toxicology (13.1)]*, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness in patients below the age of 18 years have not been established.

8.5 Geriatric Use

Of the 1169 adult cancer patients treated with AKYNZEO in clinical studies, 18% were aged 65 and over, while 2% were aged 75 years and over. The nature and frequency of adverse reactions were similar in elderly and younger patients. Exploratory analyses of the impact of age on efficacy were performed in the two trials that compared AKYNZEO to palonosetron *[see Clinical Studies (14)]*. In Study 1 in patients treated with cisplatin chemotherapy, among the patients less than age 65 years, 115 were treated with AKYNZEO and 116 were treated with palonosetron alone. Among the patients 65 years or older, 20 were treated with AKYNZEO and 20 were treated with palonosetron alone. The difference in Complete Response (CR) rates between AKYNZEO and palonosetron alone was similar between the two age groups in both the acute and delayed phases. In Study 2 in patients treated with anthracyclines plus cyclophosphamide chemotherapy, among the patients less than age 65 years, 608 were treated with AKYNZEO and 602 were treated with palonosetron alone. Among the patients 65 years or older, 116 were treated with AKYNZEO and 123 were treated with palonosetron alone. The difference in CR rates between AKYNZEO and palonosetron alone (4% in <65 years and 2% in ≥65 years) was similar between the two age groups in the acute phase. In the delayed phase, the difference in CR rates between AKYNZEO and palonosetron alone (9% in <65 years and 1% in ≥ 65 years) was numerically higher in patients <65 years. This difference between age groups in the delayed phase of Study 2 may be explained, in part, by higher CR in the delayed phase associated with palonosetron alone in the older age group (81%) relative to the younger patients treated with palonosetron alone (67%).

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.

8.6 Hepatic Impairment

No dosage adjustment for AKYNZEO is necessary for patients with mild to moderate hepatic impairment (Child-Pugh score 5 to 8). Limited data are available with AKYNZEO in patients with severe hepatic impairment (Child-Pugh score >9)/ Avoid use of AKYNZEO in patients with severe hepatic impairment. *[see Overdosage (10), Clinical Pharmacology (12.3)]*.

Reference ID: 3642902

8.7 Renal Impairment

No dosage adjustment for AKYNZEO is necessary in patients with mild to moderate renal impairment. The pharmacokinetics and safety of netupitant has not been studied in patients with severe renal impairment, although severe renal impairment did not substantially affect pharmacokinetics of palonosetron. The pharmacokinetics for netupitant and palonosetron was not studied in patients with end-stage renal disease requiring hemodialysis. Avoid use of AKYNZEO in patients with severe renal impairment or end-stage renal disease *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

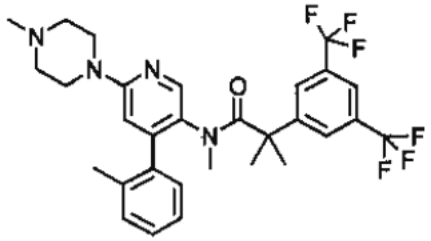
No specific information is available on the treatment of overdosage with AKYNZEO. In the event of overdose, AKYNZEO should be discontinued and general supportive treatment and monitoring should be provided. Because of the antiemetic activity of AKYNZEO, drug-induced emesis may not be effective. Dialysis studies have not been performed; due to the large volume of distribution, dialysis is unlikely to be an effective treatment for AKYNZEO overdose.

A total of 33 adult cancer patients were administered oral palonosetron at a dose of 90 µg/kg (equivalent to 6 mg fixed dose), as part of a dose ranging study. This is approximately 12 times the recommended oral dose of 0.5 mg palonosetron. 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.

11 DESCRIPTION

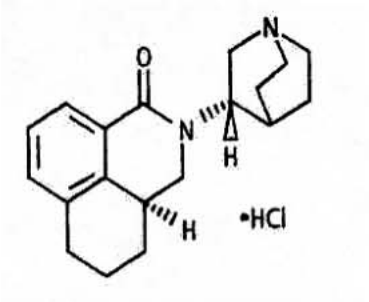
AKYNZEO (300 mg netupitant/0.5 mg palonosetron) is an oral fixed combination product of netupitant, a substance P/neurokinin 1 (NK_1) receptor antagonist, and palonosetron hydrochloride, a serotonin-3 (5-HT_3) receptor antagonist. Both netupitant and palonosetron hydrochloride are anti-nausea and anti-emetic agents.

Netupitant is chemically described: 2-[3,5-bis(trifluoromethyl)phenyl]-N, 2 dimethyl-N-[4-(2-methylphenyl)-6-(4-methylpiperazin-1-yl)pyridin-3-yl] propanamide. The empirical formula is $C_{30}H_{32}F_6N_4O$, with a molecular weight of 578.61. Netupitant exists as a single isomer and has the following structural formula:



Palonosetron hydrochloride is chemically described: (3aS)-2-[(S)-1-Azabicyclo [2.2.2]oct-3-yl]-2,3,3a,4,5,6-hexahydro-1-oxo-1H-benz[de]isoquinoline hydrochloride. The empirical formula is $C_{19}H_{24}N_2O.HCl$, with a molecular weight of 332.87. Palonosetron hydrochloride exists as a single isomer and has the following structural formula:

Reference ID: 3642902



Netupitant is 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.

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.

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). The inactive ingredients are microcrystalline cellulose, sucrose fatty acid esters, povidone K-30, croscarmellose sodium, purified water, silicon dioxide, sodium stearyl fumarate, magnesium stearate, mono- and di-glycerides of capryl/capric acid, glycerin, polyglyceryl oleate, butylated hydroxyanisole (BHA), gelatin, sorbitol, titanium dioxide, yellow iron oxide, and red iron oxide. It may contain traces of medium-chain triglycerides, lecithin, and denatured ethanol.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

Palonosetron is a 5-HT_3 receptor antagonist with a strong binding affinity for this receptor and little or no affinity for other receptors. Cancer chemotherapy may be associated with a high incidence of nausea and vomiting, particularly when certain agents, such as cisplatin, are used. 5-HT_3 receptors are located on the nerve terminals of the vagus in the periphery and centrally in the chemoreceptor trigger zone of the area postrema. Chemotherapeutic agents 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. The development of acute emesis is known to depend on serotonin and its 5-HT_3 receptors have been demonstrated to selectively stimulate the emetic response.

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

12.2 Pharmacodynamics

NK_1 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 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.

Cardiac Electrophysiology

Co-administration of single dose netupitant 600 mg and palonosetron 1.5 mg had no significant effects on the QTc interval.

12.3 Pharmacokinetics

After single dose administration of AKYNZEO in healthy subjects, the peak plasma concentrations for netupitant and palonosetron were reached in about 5 hours.

Reference ID: 3642902

Table 4: 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}[1] (h)	5 (2-12)	5 (1-12)
AUC (ng*h/mL)	14401 (51)	56.7 (33)
$T_{1/2}$ (h)	96 (61)	44 (34)

[1] 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 1 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.

No significant changes in pharmacokinetics of netupitant and palonosetron were observed when 450 mg oral netupitant and 0.75 mg oral palonosetron were co-administered.

Netupitant

Absorption

Upon oral administration of a single dose of netupitant, netupitant started to be measurable in plasma between 15 minutes and 3 hours after dosing. Plasma concentrations reached C_{max} in approximately 5 hours. There was a greater than dose-proportional increase in the systemic exposure with the dose increase from 10 mg to 300 mg and a dose-proportional increase in systemic exposure with a dose increase from 300 mg to 450 mg.

Distribution

In cancer patients netupitant disposition was characterized by a large apparent volume of distribution (Vz/F: 1982 ± 906 L) (mean ± SD). Human plasma protein binding of netupitant is greater than 99.5% at drug concentrations ranging from 10-1300 ng/mL and protein binding of its major metabolites (M1, M2 and M3) is greater than 97% at drug concentrations ranging from 100 to 2000 ng/mL.

Metabolism

Once absorbed, netupitant is extensively metabolized to form three major metabolites: desmethyl derivative, M1; N-oxide derivative, M2; and OH-methyl derivative, M3. Metabolism is mediated primarily by CYP3A4 and to a lesser extent by CYP2C9 and CYP2D6. Metabolites M1, M2 and M3 were shown to bind to the substance P/neurokinin 1 (NK_1) receptor.

Mean C_{max} was approximately 11%, 47% and 16% of netupitant for metabolites M1, M2 and M3, respectively. Mean AUC for metabolites M1, M2 and M3 was 29%, 14% and 33% of netupitant, respectively. The median t_{max} for metabolite M2 was 5 hours and was about 17-32 hours for metabolites M1 and M3.

Elimination

Netupitant is eliminated from the body in a multi-exponential fashion, with an apparent elimination half-life in cancer patients of 80 ± 29 hours (mean ± SD) and with an estimated systemic clearance of 20.3 ± 9.2 L/h (mean ± SD) after a single oral dose of AKYNZEO.

After a single oral administration of [^{14}C]-netupitant, approximately half the administered radioactivity was recovered from urine and feces within 120 hours of dosing. The total of 3.95% and 70.7% of the radioactive dose was recovered in the urine and feces collected over 336 hours, respectively, and the

Reference ID: 3642902

mean fraction of an oral dose of netupitant excreted unchanged in urine is less than 1% suggesting renal clearance is not a significant elimination route for the netupitant-related entities. About 86.5% and 4.7% of administered radioactivity was estimated to be excreted via the feces and urine in 30 days post-dose

Palonosetron

Absorption

Following oral administration, palonosetron is well absorbed with its absolute bioavailability reaching 97%. After single oral doses using buffered solution mean maximum palonosetron concentrations (C_{max}) and area under the concentration-time curve ($AUC_{0-\infty}$) were dose proportional over the dose range of 3.0 to 80 μg/kg in healthy subjects.

Distribution

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

Metabolism

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

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 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.

Specific Populations

Gender

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

Geriatrics

In cancer patients receiving AKYNZEO, population PK analysis indicated that age (within the range of 29 to 75 years old) did not influence the pharmacokinetics of netupitant or palonosetron. In healthy elderly subjects (>65 years old) the mean $AUC_{0-\infty}$ and C_{max} was 25% and 36% higher, respectively, for netupitant, and 37% and 10% higher, respectively, for palonosetron compared to those in healthy younger adults (22-45 years old).

Hepatic Impairment

The effects of hepatic impairment on the PK of netupitant and palonosetron were studied following administration of a single oral dose of AKYNZEO to patients with mild (Child-Pugh score 5 to 6), moderate (Child-Pugh score 7 to 9), or severe (Child-Pugh score >9) hepatic impairment.

Reference ID: 3642902

In patients with mild or moderate hepatic impairment, the mean $AUC_{0-\infty}$ of netupitant was 67% and 86% higher, respectively, than in healthy subjects and the mean C_{max} for netupitant was about 40% and 41% higher, respectively, than in 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 and the mean C_{max} for palonosetron was about 14% higher and unchanged, respectively, than in healthy subjects.

The pharmacokinetics of netupitant and palonosetron was available from only two patients with severe hepatic impairment. As such the data are too limited to draw a conclusion.

Renal Impairment

In a population PK analysis, mild and moderate renal impairment did not significantly affect the pharmacokinetics of netupitant in cancer patients. Netupitant has not been studied in patients with severe renal impairment.

Mild to moderate renal impairment does not significantly affect palonosetron pharmacokinetic parameters. In a study with intravenous palonosetron, total systemic exposure to palonosetron increased by approximately 28% in patients with severe renal impairment relative to healthy subjects.

The pharmacokinetics of either palonosetron or netupitant has not been studied in subjects with end-stage renal disease.

Drug Interactions: *In vitro* studies have shown that netupitant and its metabolite M1 are inhibitors of CYP3A4. An *in vivo* study has confirmed that netupitant is a moderate inhibitor of CYP3A4.

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

Netupitant and its metabolites, M1, M2 and M3, are not inducers of CYP1A2, CYP2C9, CYP2C19 and CYP3A4. Their induction potential of CYP2B6 is unknown.

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

In vitro studies, palonosetron does not inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2D6, CYP2E1 and CYP3A4/5 or induce CYP1A2, CYP2D6 or CYP3A4/5. CYP2C19 was not investigated.

Dexamethasone

Co-administration of a single dose of netupitant (300 mg) with a dexamethasone regimen (20 mg on Day 1, followed by 8 mg b.i.d. from Day 2 to Day 4) significantly increased exposure to dexamethasone. When netupitant was co-administered on Day 1, the mean AUC of dexamethasone was increased by 1.7-fold on Day 1 and up to 2.4-fold on Day 2 and Day 4.

Chemotherapeutic Agents (docetaxel, etoposide, cyclophosphamide)

Systemic exposure to intravenously administered chemotherapeutic agents that are metabolized by CYP3A4 was higher when AKYNZEO was co-administered than when palonosetron alone was co-administered in cancer patients.

With co-administration of AKYNZEO the mean C_{max} and AUC of docetaxel were 49% and 35% higher, respectively, and mean C_{max} and AUC of etoposide were increased by 10% and 28%, respectively, compared to when co-administered with palonosetron alone.

Reference ID: 3642902

Mean C_{max} and AUC for cyclophosphamide after co-administration with AKYNZEO was 27% and 20% higher compared to when co-administered with palonosetron alone.

The mean AUC of palonosetron was about 65% higher when AKYNZEO was co-administered with docetaxel than with etoposide or cyclophosphamide, while the mean AUC of netupitant was similar among groups that received docetaxel, etoposide, or cyclophosphamide.

Midazolam

When co-administered with netupitant 300 mg the mean C_{max} and AUC of midazolam after single dose oral administration of 7.5 mg midazolam was 36% and 126% higher, respectively.

Erythromycin

When 500 mg erythromycin was co-administered with netupitant 300 mg, the systemic exposure of erythromycin was highly variable and the mean C_{max} and AUC of erythromycin were increased by 92% and 56%, respectively.

Oral Contraceptives

Single dose AKYNZEO, when given with a single oral dose of 60 µg ethinyl estradiol and 300 µg levonorgestrel, increased the AUC of levonorgestrel by 46%. AKYNZEO had no significant effect on the AUC of ethinyl estradiol.

Digoxin

Co-administration of netupitant 450 mg did not significantly affect the systemic exposure and urinary excretion of digoxin, a substrate of P-glycoprotein, at steady-state. Concurrent administration of AKYNZEO with digoxin is not expected to affect the systemic exposure to digoxin.

Effects of other drugs on AKYNZEO

Rifampicin

Single dose AKYNZEO was administered with rifampicin, a strong CYP3A4 inducer, following once daily administration of 600 mg rifampicin for 17 days. Pharmacokinetics of netupitant and palonosetron were compared to that after administration of AKYNZEO alone. Co-administration of rifampicin decreased the mean C_{max} and $AUC_{0-\infty}$ of netupitant by 62% and 82%, respectively, compared to those after AKYNZEO alone. Co-administration of rifampicin decreased the mean C_{max} and AUC for palonosetron by 15% and 19%, respectively.

Ketoconazole

Single dose AKYNZEO was administered with ketoconazole, a strong CYP3A4 inhibitor, following once daily administration of 400 mg ketoconazole for 12 days. Pharmacokinetics of netupitant and palonosetron were compared to that after administration of AKYNZEO alone. Co-administration with ketoconazole increased mean C_{max} and AUC of netupitant by 25% and 140%, respectively, compared to those after administration of AKYNZEO alone. The mean AUC and C_{max} of palonosetron were 10% and 15% higher, respectively, when co-administered with ketoconazole.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Netupitant

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.

Reference ID: 3642902

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.

Palonosetron

In a 104-week carcinogenicity study in CD-1 mice, animals were treated with oral doses of palonosetron at 10, 30, and 60 mg/kg/day. Treatment with palonosetron was not tumorigenic. The highest tested dose produced a systemic exposure to palonosetron (plasma AUC) of about 90 to 173 times the human exposure (AUC=49.7 ng•h/mL) at the recommended oral dose of 0.5 mg. In a 104-week carcinogenicity study in Sprague-Dawley rats, male and female rats were treated with oral doses of 15, 30, and 60 mg/kg/day and 15, 45, and 90 mg/kg/day, respectively. The highest doses produced a systemic exposure to palonosetron (plasma AUC) of 82 and 185 times the human exposure at the recommended dose. Treatment with palonosetron produced increased incidences of adrenal benign pheochromocytoma and combined benign and malignant pheochromocytoma, increased incidences of pancreatic Islet cell adenoma and combined adenoma and carcinoma and pituitary adenoma in male rats. In female rats, it produced hepatocellular adenoma and carcinoma and increased the incidences of thyroid C-cell adenoma and combined adenoma and carcinoma.

Palonosetron was not genotoxic in the Ames test, the Chinese hamster ovarian cell (CHO/HGPRT) forward mutation test, the ex vivo hepatocyte unscheduled DNA synthesis (UDS) test, or the mouse micronucleus test. It was, however, positive for clastogenic effects in the Chinese hamster ovarian (CHO) cell chromosomal aberration test. Palonosetron at oral doses up to 60 mg/kg/day (about 921 times the recommended human oral dose based on body surface area) was found to have no effect on fertility and reproductive performance of male and female rats.

14 CLINICAL STUDIES

Oral administration of AKYNZEO in combination with dexamethasone has been shown to prevent acute and delayed nausea and vomiting associated with initial and repeat courses of chemotherapy in two trials.

Study 1

In a multicenter, randomized, parallel, double-blind, controlled clinical trial of 694 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 a chemotherapy regimen that included cisplatin (median dose=75 mg/m^2). 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 5.

Table 5: Oral Antiemetic Treatment Regimen in the Highly Emetogenic Chemotherapy Study

Treatment Regimen	Day 1	Days 2 to 4
AKYNZEO	AKYNZEO 300 mg neupitant/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

Of the 135 patients who received AKYNZEO, 43% were women, and all patients were White. The age ranged from 19 to 77 years, with a median age of 53 years.

During the study, 86% of the 135 treated patients in the AKYNZEO arm received a concomitant chemotherapeutic agent in addition to protocol-mandated cisplatin. The most common chemotherapeutic agents and the proportion of patients exposed were cyclophosphamide (34%), fluorouracil (24%), etoposide (21%), and doxorubicin (16%).

Reference ID: 3642902

The key efficacy endpoints were complete response (CR) (defined as no emetic episode and no use of rescue medication) for the 25-120 hour interval (delayed phase), CR for the 0-24 hour interval (acute phase), and CR within 120 hours (overall phase) after the start of the chemotherapy administration.

A summary of the key results from this study is shown in Table 6.

Table 6: Proportion of Patients Responding by Treatment Group and Phase in Study 1

	AKYNZEO 300 mg netupitant/ 0.5 mg palonosetron N=135 %	Palonosetron 0.5 mg N=136 %	p-value*
COMPLETE RESPONSE			
Delayed Phase†	90.4	80.1	0.032
Acute Phase‡	98.5	89.7	0.002
Overall Phase§	89.6	76.5	0.003

*Adjusted p-values for multiple comparisons using Cochran-Mantel-Haenszel test, stratified by gender.
†Delayed phase: 25 to 120 hours post-cisplatin treatment.
‡Acute phase: 0 to 24 hours post-cisplatin treatment.
§Overall: 0 to 120 hours post-cisplatin treatment.

Study 2

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 (Study 2). All patients received a single oral dose of dexamethasone.

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

Table 7: Oral Antiemetic Treatment Regimen in Study 2

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=725; palonosetron n=725) received study medication: of these, 1438 patients (98.8%) completed cycle 1 and 1286 patients (88.4%) continued treatment in the multiple-cycle extension. A total of 907 patients (62.3%) completed the multiple-cycle extension up to a maximum of eight treatment cycles.

Of the 725 patients who received AKYNZEO, 711 (98%) were women; 79% were White, 14% Asian, 6% Hispanic, and <1% were Black or Other. Age ranged from 22 to 79 years, with a median age of 54 years. A total of 724 patients (99.9%) were treated with cyclophosphamide. All patients were additionally treated with either doxorubicin (68.0%) or epirubicin (32.0%).

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

Reference ID: 3642902

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

Major secondary efficacy endpoints included CR for the acute and overall phases.

A summary of key results from Study 2 is shown in Table 8.

Table 8 Proportion of Patients Responding by Treatment Group and Phase – Cycle 1 in Study 2

	AKYNZEO 300 mg netupitant/ 0.5 mg palonosetron N=724 %	Palonosetron 0.5 mg N=725 %	p-value*
PRIMARY ENDPOINT			
COMPLETE RESPONSE			
Delayed Phase†	76.9	69.5	0.001
MAJOR SECONDARY ENDPOINTS			
COMPLETE RESPONSE			
Acute Phase‡	88.4	85.0	0.047
Overall Phase§	74.3	66.6	0.001

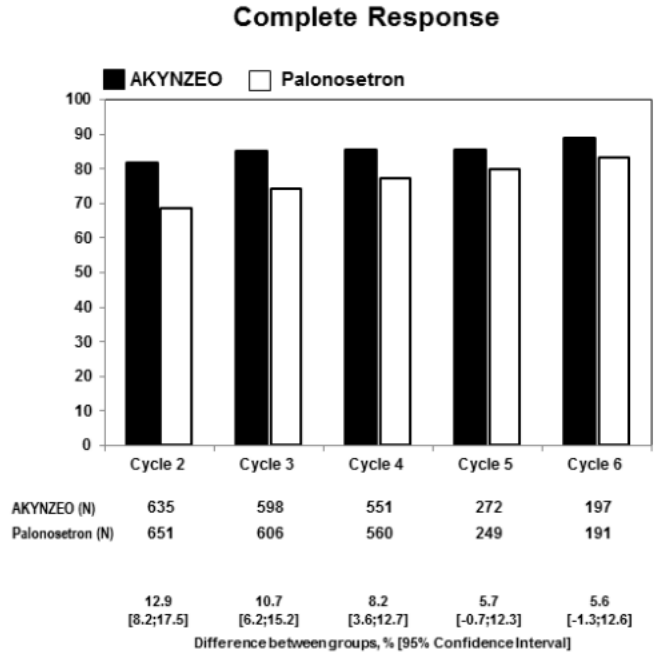
*p-value from Cochran-Mantel-Haenszel test, stratified by age class and region.
‡Acute phase: 0 to 24 hours after anthracycline and cyclophosphamide regimen.
†Delayed phase: 25 to 120 hours after anthracycline and cyclophosphamide regimen.
§Overall: 0 to 120 hours after anthracycline and cyclophosphamide regimen.

Multiple cycles

Patients continued into the Multiple-Cycle extension for up to 7 additional cycles of chemotherapy. The proportion of patients with complete response in the delayed phase by treatment group at each cycle (cycles 2 to 6) is displayed in Figure 1. A limited number of patients received treatment beyond cycle 6. During all cycles the CR rate 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.

Reference ID: 3642902

Figure 1: Proportion of Patients with Complete Response in the Delayed Phase by Treatment Group and Cycle in Study 2



Additional clinical trials (Study 3 and Study 4) were conducted to support the efficacy of AKYNZEO.

Study 3

In a separate study, 309 patients undergoing initial and repeat cycles of chemotherapy (including carboplatin, cisplatin, oxaliplatin, and doxorubicin regimens) received AKYNZEO; efficacy was maintained throughout all cycles.

Study 4

In one multicenter, multinational, randomized, active-controlled, double-blind, double-dummy, parallel group, clinical non-inferiority study, the efficacy and safety of a single dose of oral palonosetron 0.50 mg was compared to intravenous palonosetron 0.25 mg in cancer patients scheduled to receive highly emetogenic cisplatin ($\geq$70 mg/m^2) based chemotherapy. The purpose of this study was to demonstrate that oral palonosetron 0.5 mg contributes to the efficacy of AKYNZEO during the acute phase (first 24 hours after cancer chemotherapy) in the setting of cisplatin based chemotherapy. A total of 739 patients (oral palonosetron n=370; intravenous palonosetron n=369) received study medication.

The primary efficacy endpoint was complete response (CR) (defined as no emetic episode and no use of rescue medication) within 24 hours (acute phase) after the start of cisplatin-based chemotherapy administration. In the oral palonosetron arm, 89.4% of patients achieved a CR in the acute phase compared to 86.2% of patients in the intravenous palonosetron arm, with a difference of 3.21% (99% CI: -2.74% to 9.17%). Non-inferiority of oral palonosetron versus intravenous palonosetron was demonstrated since the lower limit of the two-sided 99% CI for the difference in proportions of patients with CR was greater (i.e., closer to zero) than the pre-defined non-inferiority margin set at -15%.

16 HOW SUPPLIED/STORAGE AND HANDLING

NDC # 62856-796-01, AKYNZEO (300 mg netupitant/0.5 mg palonosetron). AKYNZEO is supplied as hard gelatin capsules with white body and caramel cap with "HE1" printed on the body, one capsule per blister.

Reference ID: 3642902

Storage

Store at 20 °C to 25 °C (68 °F to 77 °F); excursions permitted from 15 °C to 30 °C (59 °F to 86 °F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise patients to read the FDA-approved patient labeling (Patient Information).

Administration

Advise patients to take AKYNZEO with or without food approximately 1 hour prior to the start of chemotherapy.

Hypersensitivity Reactions

Advise patients that hypersensitivity reactions, including anaphylaxis, have been reported in patients receiving palonosetron. Advise patients to seek immediate medical attention if any signs or symptoms of a hypersensitivity reaction occur while taking AKYNZEO.

Serotonin Syndrome

Advise patients of the possibility of serotonin syndrome especially with concomitant use of AKYNZEO and another serotonergic agent such as medications to treat depression and migraines. Advise patients to seek immediate medical attention if the following symptoms occur: changes in mental status, autonomic instability, neuromuscular symptoms, with or without gastrointestinal symptoms *[see Warnings and Precautions (5.2)]*.

Jointly manufactured by Catalent Pharma Solutions, Somerset, NJ and Helsinn Birex Pharmaceuticals, Dublin, Ireland for Helsinn Healthcare SA, Switzerland

Distributed and marketed by Eisai Inc., Woodcliff Lake, NJ 07677, under license of Helsinn Healthcare SA, Switzerland

AKYNZEO is a registered trademark of Helsinn Healthcare, SA, Lugano, Switzerland

© 2014 Eisai Inc., Woodcliff Lake, NJ 07677 U.S.A. 201227

Patient Information
AKYNZEO® (a kin zee oh)
(netupitant and palonosetron) capsules

Read this Patient Information before you take AKYNZEO and each time you take AKYNZEO. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment.

What is AKYNZEO?

AKYNZEO is a prescription medicine called an "antiemetic." AKYNZEO is used in people to help prevent the nausea and vomiting that happens right away or later with certain anti-cancer medicines (chemotherapy).

It is not known if AKYNZEO is safe and effective in children under 18 years of age.

What should I tell my doctor before taking AKYNZEO?

Before taking AKYNZEO, tell your doctor about all of your medical conditions, including if you:

- have had an allergic reaction to palonosetron or another medicine for nausea or vomiting.
- have liver problems.
- are pregnant or plan to become pregnant. It is not known if AKYNZEO will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if AKYNZEO passes into your breast milk. You and your doctor should decide if you will take AKYNZEO or breastfeed. You should not do both.

Tell your doctor about all of the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How should I take AKYNZEO?

- Take AKYNZEO exactly as your doctor tells you to take it.
- Take 1 AKYNZEO capsule by mouth, about 1 hour before you get your anti-cancer medicine (chemotherapy).
- Take AKYNZEO with or without food.
- If you take too much AKYNZEO, call your doctor or go to the nearest emergency room right away.

What are the possible side effects of AKYNZEO?

AKYNZEO may cause serious side effects, including:

- **Allergic reactions**, such as anaphylaxis. Get emergency medical help right away if you get any of the following symptoms of a serious allergic reaction with AKYNZEO: hives, swollen face, trouble breathing, or chest pain.
- **Serotonin syndrome** which can happen with AKYNZEO particularly with certain other medicines such as anti-depressants and anti-migraine medicines and can lead to death. Go to the nearest hospital emergency room right away if you get any of the following symptoms: agitation, hallucinations or other changes in mental status, dizziness, muscle twitching (overactive reflexes), or seizures.

The most common side effects of AKYNZEO are headache, weakness, fatigue, upset stomach, constipation, and skin redness.

These are not all the possible side effects of AKYNZEO. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store AKYNZEO?

Store AKYNZEO at room temperature between 68 °F to 77 °F (20 °C to 25 °C).

General information about the safe and effective use of AKYNZEO

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use AKYNZEO for a condition for which it was not prescribed. Do not give AKYNZEO to other people, even if they have the same symptoms you have. It may harm them. You can ask your doctor or pharmacist for information about AKYNZEO that is written for health professionals.

What are the ingredients in AKYNZEO?

Active ingredients: netupitant and palonosetron hydrochloride

Inactive ingredients: microcrystalline cellulose, sucrose fatty acid esters, povidone K-30, croscarmellose sodium, purified water, silicon dioxide, sodium stearyl fumarate, magnesium stearate, mono- and di-glycerides of capryl/capric acid, glycerin, polyglyceryl oleate, butylated hydroxyanisole (BHA), gelatin, sorbitol, titanium dioxide, yellow iron oxide, red iron oxide. AKYNZEO may contain small amounts of medium-chain triglycerides, lecithin, and denatured ethanol.

Jointly manufactured by Catalent Pharma Solutions, Somerset, NJ and Helsinn Birex Pharmaceuticals, Dublin, Ireland

for Helsinn Healthcare SA, Switzerland
Distributed and marketed by Eisai Inc. Woodcliff Lake, NJ 07677 under license of Helsinn Healthcare SA, Switzerland
AKYNZEO is a registered trademark of Helsinn Healthcare SA, Lugano, Switzerland
© 2014 Eisai Inc., Woodcliff Lake, NJ 07677 U.S.A. 201227 For more information, go to www.akynzeo.com

This Patient Information has been approved by the U.S. Food and Drug Administration. **Issued: October 2014**

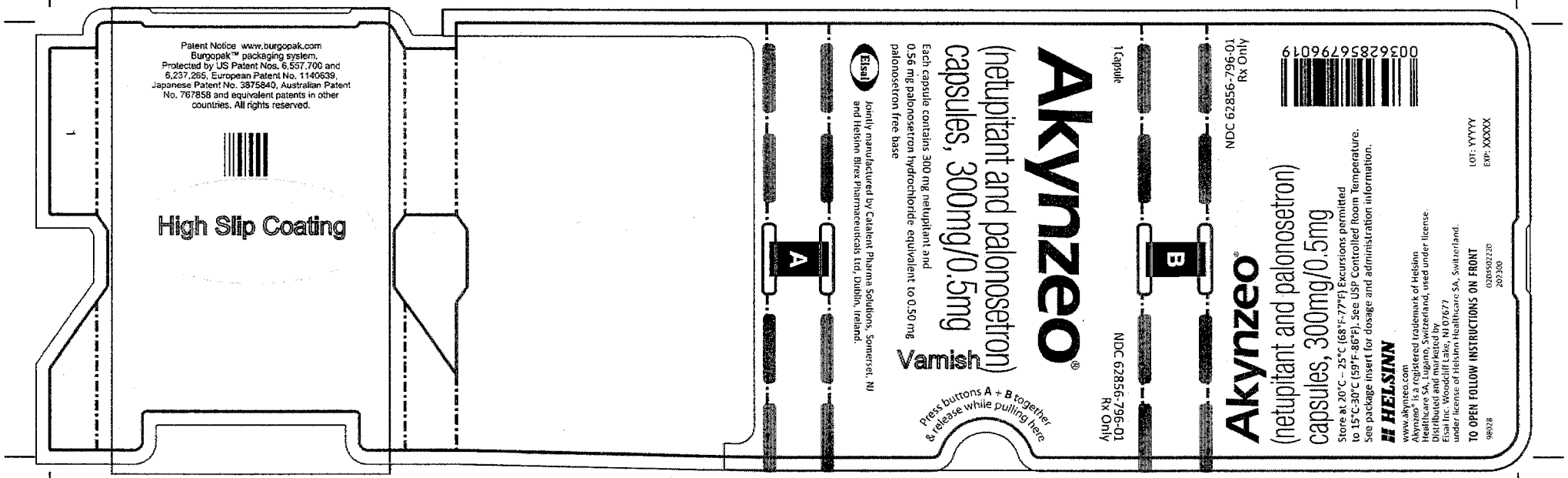
Instructions for opening the AKYNZEO pack:

1. Press buttons A and B together with one hand.	
2. Pull the tab card on the right hand side with other hand.	
3. Release buttons A and B while pulling the tab card.	
4. Keep pulling the tab card until the pack is fully open.	

(b) (4)

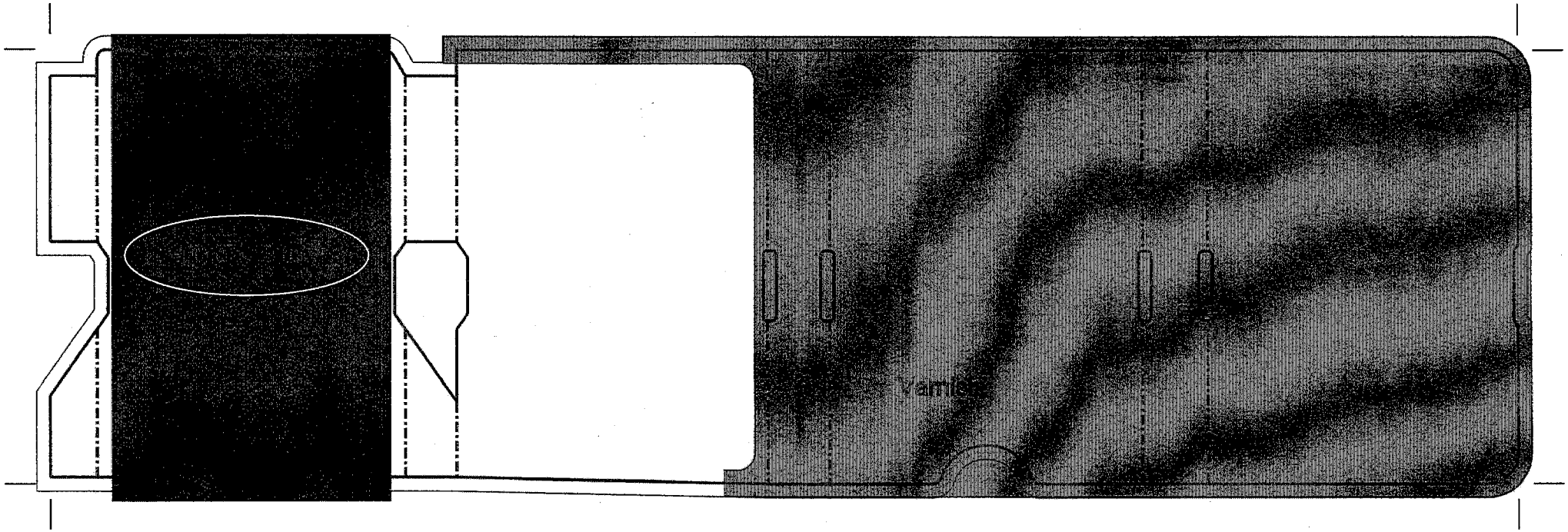
Reference ID: 3638364

OUTSIDE VARNISH COATING



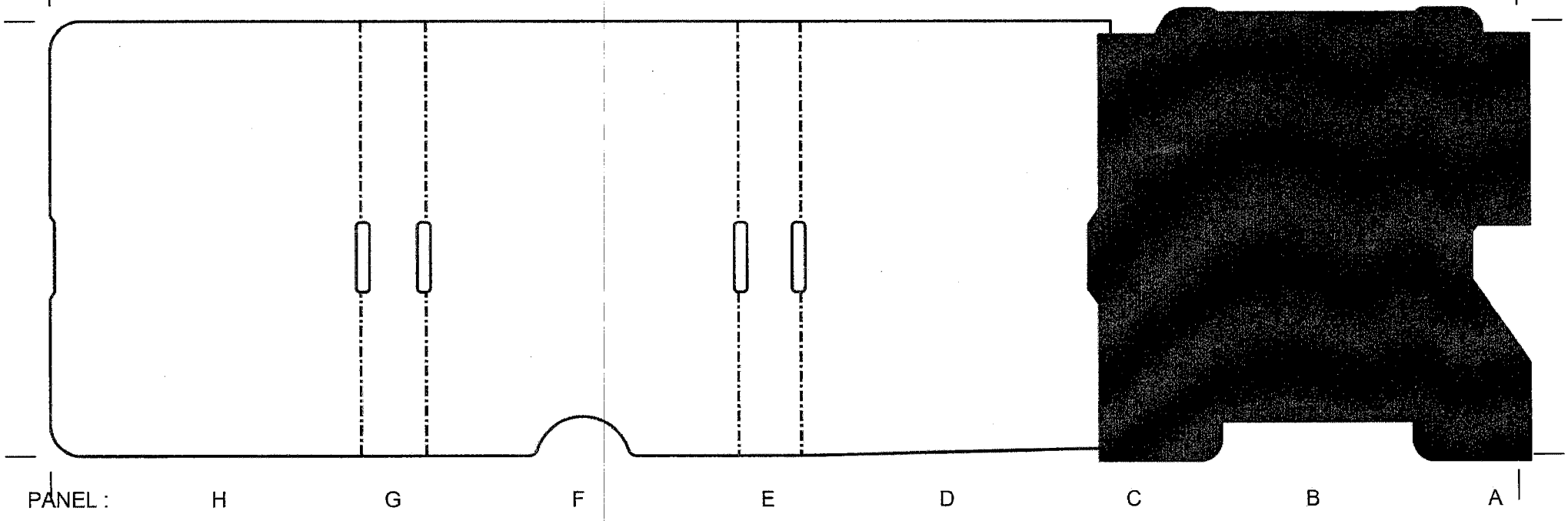
A PANEL : B C D E F G H

b(4)



b(4)

INSIDE VARNISH COATING



b(4)

Reference ID: 3638364

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JULIE G BEITZ
10/10/2014