Eisai Inc. Medical Information
100 Tice Blvd Woodcliff Lake, NJ 07677
1-888-274-2378 • Fax: 732-791-1399 • http://www.eisai.com/us

January 22, 2015

Dear Montana Medicaid:

Thank you for your interest in **AKYNZEO®** *(netupitant and palonosetron)*. Per your request to Eisai Inc., we are enclosing specific information you requested.

AKYNZEO® (netupitant/palonosetron HCl) – Formulary Dossier

Please note that AKYNZEO is approved for those indications and dosages that appear in the enclosed AKYNZEO Full Prescribing Information. The enclosed information and/or its appendices may summarize publications or guidelines that describe indications or treatment modalities for the use of AKYNZEO that have not been approved by the Food and Drug Administration.

The enclosed information is provided by Eisai Inc. as a service to healthcare professionals and is intended to assist you in forming your own clinical conclusions regarding the use of Eisai products. Eisai Inc. does not recommend or endorse the use of this product in any manner other than as described in the Full Prescribing Information.

INDICATION

AKYNZEO is a fixed combination of netupitant, a substance P/neurokinin 1 (NK1) receptor antagonist, and palonosetron, a serotonin-3 (5-HT3) 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.

IMPORTANT SAFETY INFORMATION

Warning and Precautions

- Hypersensitivity reactions, including anaphylaxis, have been reported with or without known hypersensitivity to other 5-HT3 receptor antagonists
- Serotonin syndrome has been reported with 5-HT3 receptor antagonists alone but particularly with the use of serotonergic drugs. Symptoms associated with serotonin syndrome may include the following combination of signs and symptoms: mental status changes, autonomic instability, neuromuscular symptoms, seizures, and gastrointestinal symptoms. Patients should be monitored for the emergence of serotonin syndrome, and if symptoms occur, discontinue AKYNZEO and initiate supportive treatment

Adverse Reactions

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

Drug Interactions

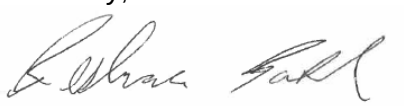
- Use with caution in patients receiving concomitant medications primarily metabolized by CYP3A4. The inhibitory effect on CYP3A4 can last for multiple days
    - Dexamethasone doses should be reduced when given with AKYNZEO
    - Consider the potential effects of increased plasma concentrations of midazolam or other benzodiazepines metabolized via CYP3A4 (alprazolam, triazolam) when administering with AKYNZEO
    - Caution and monitoring for chemotherapy-related adverse events are advised in patients receiving chemotherapy agents metabolized primarily by CYP3A4 including docetaxel, paclitaxel, etoposide, irinotecan, cyclophosphamide, ifosfamide, imatinib, vinorelbine, vinblastine, and vincristine
- Avoid concomitant use of AKYNZEO in patients on chronic use of a strong CYP3A4 inducer such as rifampin as this may decrease the efficacy of AKYNZEO

Use in Specific Populations

- Avoid use of AKYNZEO in patients with severe hepatic impairment, severe renal impairment, or end stage renal disease

Thank you for the opportunity to respond to your inquiry, and for your interest in AKYNZEO.

Sincerely,



Reshma Patel, PharmD
Medical Information Manager, Medical Information

SR#: 00071184

Enclosures: AKYNZEO Full Prescribing Information; Formulary Dossier

AKYNZEO®

(netupitant/palonosetron) Capsules

EISAI INC.
100 Tice Boulevard
Woodcliff Lakes, NJ 07677

TABLE OF CONTENTS

SUBJECT	PAGE
GLOSSARY OF TERMS	**4**
SECTION I: EXECUTIVE SUMMARY	**6**
SECTION II: DISEASE DESCRIPTION AND PRODUCT INFORMATION	**9**
Introduction to Chemotherapy-Induced Nausea and Vomiting	**10**
Product Information for AKYNZEO	**17**
Comparison of 5-HT_3 Receptor Antagonists for the Prevention of CINV	**23**
Comparison of NK_1 Receptor Antagonists for the Prevention of CINV	**27**
Place of AKYNZEO in Therapy	**29**
SECTION III: SUPPORTING CLINICAL EVIDENCE	**34**
Clinical Studies	**36**
Supporting Clinical Evidence Table	**50**
Summary of Evidence From Secondary Sources	**57**
SECTION IV: ECONOMIC VALUE AND MODELING REPORT	**58**
SECTION V: OTHER SUPPORTING EVIDENCE	**60**
SECTION VI: SUPPORTING INFORMATION	**62**
References	**63**
Prescribing Information	**66**

This dossier is provided in response to your unsolicited request to Eisai Inc. for a formulary submission document for AKYNZEO® (netupitant/palonosetron) capsules.

In addition to published data and the full Prescribing Information, this dossier contains information not included in the full Prescribing Information as well as unpublished data. These data are provided to assist pharmacist and physician managed-care decision makers in formulary and coverage evaluations.

This dossier is intended for use only by this health plan, and its distribution and/or duplication is prohibited. Please consult the enclosed full Prescribing Information for complete safety and prescribing information for AKYNZEO®.

If you have any additional questions, please contact Eisai Medical Information:

Phone: 1-888-274-2378
Email: esi_medinfo@eisai.com
Visit us at: www.eisai.com/us

GLOSSARY OF TERMS

5-HT	5-hydroxytryptamine/serotonin
$5\text{-}HT_3$	serotonin receptor subtype 3
A/C	anthracycline/cyclophosphamide
AE	adverse event
AHFS	American Hospital Formulary Service
ALT	alanine aminotransferase
ASCO	American Society of Clinical Oncology
ASP	average sales price
AST	aspartate aminotransferase
AV	atrioventricular
BID	bis in die (Latin for “twice a day” or “twice daily”)
CI	confidence interval
CINV	chemotherapy-induced nausea and vomiting
CP	complete protection
CR	complete response
CTnI	cardiac troponin level
CTZ	chemoreceptor trigger zone
CV	cardiovascular
CYP	cytochrome P450
D_2	dopamine D2 receptor
DB	double blind
DD	double dummy
DEX	dexamethasone
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ER	emergency room
ESMO	European Society for Medical Oncology
FAS	full analysis set
FDA	Food and Drug Administration
FLIE	Functional Living Index–Emesis
GI	gastrointestinal
H_2	histamine H_2 receptor
HEC	highly emetogenic chemotherapy
HR	hazard ratio
IM	intramuscular
INR	International Normalized Ratio
ITT	intent to treat
IV	intravenous
KPS	Karnofsky performance status
LEC	low emetogenic chemotherapy
LVEF	left ventricular ejection fraction
M_1	muscarinic acetylcholine receptor 1
MASCC	Multinational Association of Supportive Care in Cancer
MC	multicenter
MEC	moderately emetogenic chemotherapy
MN	multinational
ms	millisecond
NCCN	National Comprehensive Cancer Network
NDC	National Drug Code
NEPA	netupitant/palonosetron

NIDL	no impact on daily living
NK_1	neurokinin 1
NV	nausea and vomiting
ODT	orally disintegrating tablet
OR	odds ratio
PG	parallel group
PMPM	per member per month
PO	per os (Latin for “by mouth” or “orally”)
PP	per protocol
PPI	proton pump inhibitor
PS	performance status
QOL	quality of life
QTc	corrected QT interval
QTcB	Bazett corrected QT interval
QTcF	Fridericia corrected QT interval
R	randomized
RA	receptor antagonist
SNRI	serotonin and norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
US	United States
VAS	visual analog scale
VC	vomiting center
WAC	wholesale acquisition cost

SECTION I:
Executive Summary
for AKYNZEO®
(netupitant/palonosetron) Capsules

EXECUTIVE SUMMARY

This dossier describes AKYNZEO®, an oral fixed dose combination of two antiemetic agents—netupitant, a substance P/neurokinin 1 (NK_1) receptor antagonist, and palonosetron, a serotonin receptor subtype 3 ($5\text{-}HT_3$) antagonist.[1] The combination of netupitant and palonosetron targets two key pathways involved in the pathogenesis of acute (0 – 24 hours) and delayed (24 – 120 hrs) chemotherapy-induced nausea and vomiting (CINV).[2,3]

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 (HEC).[1] 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.

CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING

Prevention of CINV is an important component of supportive care for patients receiving cytotoxic chemotherapy. Uncontrolled CINV can have significant clinical and economic consequences as well as an adverse impact on quality of life (QOL).[4,5] CINV is commonly classified as acute and delayed. ***Acute CINV*** commonly occurs within a few minutes to several hours after chemotherapy administration (eg, oxaliplatin, temozolomide) and usually resolves within the first 24 hours. ***Delayed CINV*** occurs more than 24 hours after chemotherapy administration and may persist for 6 to 7 days after chemotherapy. Delayed CINV often occurs with the administration of agents such as cisplatin, carboplatin, cyclophosphamide, and/or doxorubicin.[4] The goal of antiemetic therapy is to prevent CINV across the entire period of risk.[4,6]

The choice of antiemetic therapy is based primarily on the intrinsic emetogenicity of the chemotherapy regimen and the potential for CINV.[4,6] In the absence of antiemetic prophylaxis, HEC leads to CINV in ≥ 90% of treated patients. Moderately emetogenic chemotherapy (MEC) causes CINV in 30% to 90% of treated patients.[7] Evidence-based treatment guidelines for the prevention of CINV recommend combination antiemetic therapy targeting different neuronal pathways involved in stimulating nausea and vomiting.[4,8,9]

Despite considerable progress in recent years, prevention of CINV remains a challenge. The incidence and severity of CINV are frequently underestimated by health care providers, and adherence to evidence-based antiemetic guidelines is suboptimal in clinical practice.[5,10] Compliance with guideline recommendations for the use of NK_1 receptor antagonists is particularly poor.[5] Prevention of delayed CINV, specifically delayed nausea, remains a significant challenge.[11]

AKYNZEO CLINICAL BENEFITS

AKYNZEO is a combination of two antiemetic agents, the NK_1 receptor antagonist netupitant and the $5\text{-}HT_3$ receptor antagonist palonosetron, in a single oral dosage form.[1] This combination may provide convenience for both patients and prescribers.

In *in vitro* studies, netupitant and palonosetron have been shown to exhibit an additive inhibitory effect on substance P-mediated responses.[12] This may result from the direct effect of netupitant on the NK_1 receptor and the ability of palonosetron to indirectly inhibit the NK_1 receptor via inhibition of $5\text{-}HT_3/NK_1$ receptor crosstalk.[13] The enhanced inhibition of substance P-mediated responses prompted the development of a fixed-dose combination of netupitant and palonosetron in a single oral formulation.[14]

In clinical trials, AKYNZEO was shown to be effective for the prevention of acute and delayed CINV after treatment with HEC or anthracycline/cyclophosphamide (A/C) chemotherapy.

- Among patients treated with HEC, overall (0 – 120 hours) complete response (CR; defined as no emesis and no rescue medication use) rates were significantly greater in patients treated with AKYNZEO compared to those treated with palonosetron (89.6% vs 76.5%, respectively; $p = 0.004$).[14] CR rates were also significantly greater in the AKYNZEO group compared with the palonosetron group in the acute (98.5% vs 89.7%; $p \leq 0.01$) and delayed phases (90.4% vs 80.1%; $p \leq 0.05$).

- In the A/C setting, CR rates in the AKYNZEO group were significantly greater than those in the palonosetron group in the delayed (76.9% vs 69.5%; p = 0.001), acute (88.4% vs 85%; p = 0.047), and overall (74.3% vs 66.6%; p = 0.001) phases.[15]
- Most common adverse reactions (incidence ≥ 3% and greater than palonosetron) in patients treated with AKYNZEO were headache, asthenia, dyspepsia, fatigue, constipation, and erythema.[1]

Inadequately controlled CINV significantly impairs QOL and patients' abilities to perform daily functions.[16,17] In a study of patients receiving A/C chemotherapy, a greater proportion of those treated with AKYNZEO reported no impact on daily living with respect to nausea, vomiting, and combined nausea/vomiting compared to those treated with palonosetron during the overall phase.[15]

The antiemetic efficacy of AKYNZEO was maintained over repeated cycles of HEC and MEC, with CR rates ranging from 81% to 92% across 6 cycles of chemotherapy.[18] The safety profile of AKYNZEO was comparable to that of aprepitant and palonosetron in patients undergoing initial and repeat cycles (median 5 cycles, range 1 to 14 cycles) of chemotherapy, including carboplatin, cisplatin, oxaliplatin, and doxorubicin regimen.[1] The most frequently reported AKYNZEO-related adverse events (AEs) included constipation (3.6%) and headache (1.0%); there was no indication of increasing AEs over multiple cycles.[18] Please see **Section II, Product Information** for AKYNZEO warnings and precaution, adverse drug reactions and drug interactions.

AKYNZEO ECONOMIC BENEFITS

Please contact Eisai Medical Information at 1-888-274-2378 for additional information.

CONCLUSIONS

AKYNZEO is a single-dose oral antiemetic combination targeting two critical antiemetic pathways. AKYNZEO has demonstrated statistically superior CR rates and comparable safety vs oral palonosetron in HEC and A/C-based regimens across multiple cycles.

SECTION II:
Disease Description and Product Information
for AKYNZEO®
(netupitant/palonosetron) Capsules

INTRODUCTION TO CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING

Nausea and vomiting are among the major side effects of cytotoxic chemotherapy. Among patients beginning cancer treatment, chemotherapy-induced nausea and vomiting (CINV) is ranked as one their greatest fears.[6,19] Inadequately controlled CINV can significantly impair a patient's QOL, increase medical costs and the use of health care resources, and lead to poor compliance with further chemotherapy.[5,6,17,20,21]

There are several distinct types of CINV, with the most common being acute, delayed, anticipatory, breakthrough, and refractory (**Table II-1**).[4]

Table II-1. Classification of Chemotherapy-Induced Nausea and Vomiting (CINV)[4]

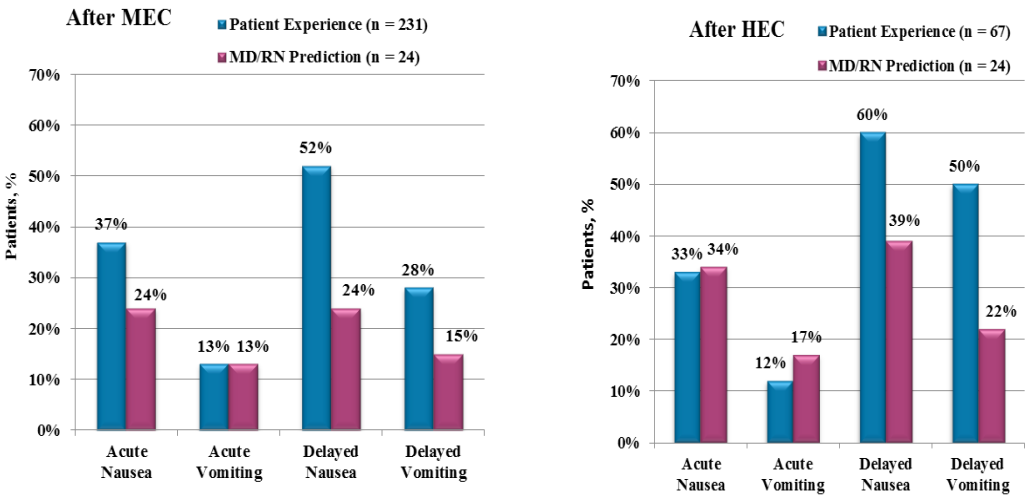
Type of CINV	Characteristics
Acute	• Commonly occurs within a few minutes to several hours after chemotherapy (eg, oxaliplatin, temozolomide) • Peaks in the first 5 to 6 hours after chemotherapy • Usually resolves within 24 hours
Delayed	• Occurs more than 24 hours after chemotherapy • More likely to occur with certain types of chemotherapy, such as cisplatin, carboplatin, cyclophosphamide, and/or doxorubicin • CINV associated with cisplatin usually peaks 48 to 72 hours after chemotherapy and may last 6 to 7 days
Anticipatory	• Occurs before a patient's next chemotherapy treatment • Commonly occurs as a result of a previous negative chemotherapy experience
Breakthrough	• Occurs despite prophylactic treatment and/or requires rescue medication
Refractory	• Occurs during subsequent cycles of chemotherapy when antiemetic prophylaxis and/or rescue medication have failed in earlier cycles

Epidemiology

In the absence of prophylactic therapy, approximately 70% to 80% of patients with cancer receiving cytotoxic chemotherapy will experience nausea and/or vomiting.[22] Significant advances in the prevention of CINV occurred in the 1990s with the approval of several 5-HT_3 receptor antagonists.[6] In 2003, approval of the long-acting 5-HT_3 antagonist palonosetron and the first NK_1 receptor antagonist, aprepitant, led to further improvements. However, CINV remains a problem. Despite the use of prophylactic antiemetic therapy, 36% to 64% of patients receiving cytotoxic chemotherapy still experience CINV.[10,16,17] Delayed CINV remains a particular challenge, with 33% of patients reporting delayed vomiting and 62% reporting delayed nausea in a community-based observational study.[16]

An international, prospective, observational study found that health care professionals tend to underestimate the incidence of CINV in their practices.[10] More than 75% of physicians and nurses underestimated the incidence of delayed CINV. The actual rate of delayed CINV was shown to be approximately twice that estimated by health care professionals (**Figure II-1**).

Figure II-1. Physician and Nurse Prediction and Patient Experiences of CINV[10]



CINV = chemotherapy-induced nausea and vomiting; HEC = highly emetogenic chemotherapy; MD = physician; MEC = moderately emetogenic chemotherapy; RN = nurse

Relevant Risk Factors

Both patient- and chemotherapy-specific risk factors affect the incidence and severity of CINV (**Table II-2**).[6] Women and younger patients (< 50 years of age) have the greatest risk of developing CINV. In addition, patients who experience CINV have a greater risk of developing CINV with subsequent chemotherapy cycles. A retrospective analysis of patients with cancer in a community-based setting showed that patients who experienced CINV during their first cycle of chemotherapy were approximately 3 to 4 times more likely to experience CINV during the subsequent 6 months of treatment.[23]

Table II-2. Risk Factors for the Development of CINV[4,6]

Chemotherapy-Specific Factors	Patient-Specific Factors
• Greater emetogenic potential of chemotherapy agent • Dose and dosage regimens • Schedule and route of administration	• Age < 50 years • Female • Low alcohol consumption* • Prior CINV • History of motion sickness • History of morning sickness • High level of pretreatment anxiety

CINV = chemotherapy-induced nausea and vomiting
*Little or no alcohol consumption.

The primary chemotherapy-specific risk factor for CINV is the intrinsic emetogenicity of the chemotherapy agent.[4] A commonly used classification system of the emetogenic potential of cytotoxic chemotherapy agents is shown in **Table II-3**.

Table II-3. Classification of Emetogenic Potential of Chemotherapy Agents[7]

Classification	Description
High	≥ 90% of patients experience CINV
Moderate	30% to 90% of patients experience CINV
Low	10% to 30% of patients experience CINV
Minimal	< 10% of patients experience CINV

CINV = chemotherapy-induced nausea and vomiting

The National Comprehensive Cancer Network (NCCN) classification of the the emetogenic potential of intravenous (IV) chemotherapy agents is shown in **Table II-4**.

Table II-4. Emetogenic Potential of IV Chemotherapeutic Agents (Adapted From the NCCN Guidelines for Antiemesis*)[4]

High Emetogenic Risk[†] (> 90%[‡])	Moderate Emetogenic Risk (30% to 90%[‡])	Low Emetogenic Risk (10% to 30%[‡])	Minimal Emetogenic Risk (< 10%[‡])
• Anthracycline (doxorubicin or epirubicin) and cyclophosphamide combination (A/C) • Carmustine > 250 mg/m^2 • Cisplatin • Cyclophosphamide > 1500 mg/m^2 • Dacarbazine • Doxorubicin ≥ 60 mg/m^2 • Epirubicin > 90 mg/m^2 • Ifosfamide ≥ 2 g/m^2 per dose • Mechlorethamine • Streptozocin	• Aldesleukin > 12 million to 15 million IU/m^2 • Amifostine > 300 mg/m^2 • Arsenic trioxide • Azacitidine • Bendamustine • Busulfan • Carboplatin[§] • Carmustine[§] ≤ 250 mg/m^2 • Clofarabine • Cyclophosphamide ≤ 1500 mg/m^2 • Cytarabine > 200 mg/m^2 • Dactinomycin[§] • Daunorubicin[§] • Doxorubicin[§] < 60 mg/m^2 • Epirubicin[§] ≤ 90 mg/m^2 • Idarubicin • Ifosfamide[§] < 2 g/m^2 per dose • Interferon α ≥ 10 million IU/m^2 • Irinotecan[§] • Melphalan • Methotrexate[§] ≥ 250 mg/m^2 • Oxaliplatin • Temozolomide	• Ado-trastuzumab emtansine • Aldesleukin ≤ 12 million IU/m^2 • Amifostine ≤ 300 mg/m^2 • Brentuximab vedotin • Cabazitaxel • Carfilzomib • Cytarabine (low dose) 100 mg/m^2 to 200 mg/m^2 • Docetaxel • Doxorubicin (liposomal) • Eribulin • Etoposide • 5-Fluorouracil • Floxuridine • Gemcitabine • Interferon α > 5 million but < 10 million IU/m^2 • Ixabepilone • Methotrexate > 50 but < 250 mg/m^2 • Mitomycin • Mitoxantrone • Omacetaxine • Paclitaxel • Paclitaxel-albumin • Pemetrexed • Pentostatin • Pralatrexate • Romidepsin • Thiotepa • Topotecan • Ziv-aflibercept	• Alemtuzumab • Asparaginase • Bevacizumab • Bleomycin • Bortezomib • Cetuximab • Cladribine (2-chlorodeoxyadenosine) • Cytarabine < 100 mg/m^2 • Decitabine • Denileukin diftitox • Dexrazoxane • Fludarabine • Interferon α ≤ 5 million IU/m^2 • Ipilimumab • Methotrexate ≤ 50 mg/m^2 • Nelarabine • Ofatumumab • Panitumumab • Pegaspargase • Peginterferon • Pertuzumab • Rituximab • Temsirolimus • Trastuzumab • Valrubicin • Vinblastine • Vincristine • Vincristine (liposomal) • Vinorelbine

IU = international units; IV = intravenous; NCCN = National Comprehensive Cancer Network
*Please refer to www.NCCN.org for complete and current information.
[†]Continuous infusion may make this agent less emetogenic.
[‡]Emetogenic potential of chemotherapeutic agent without antiemetic prophylaxis.
[§]These agents may be highly emetogenic in certain patients.

Pathophysiology

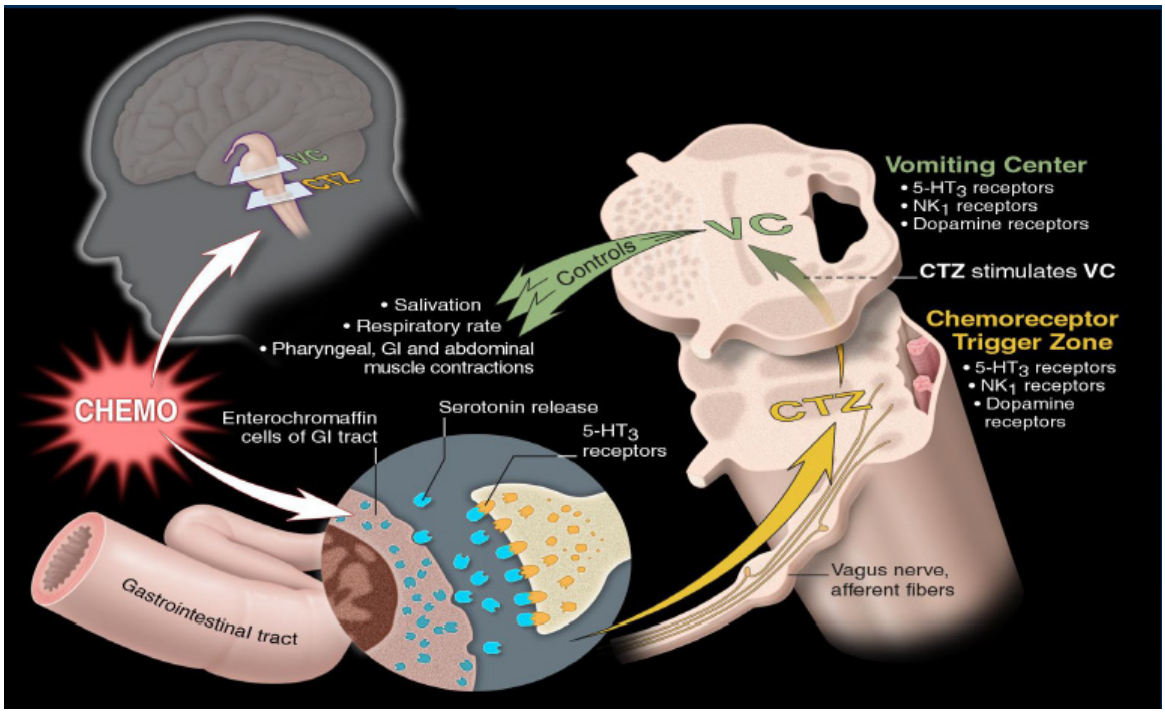
The underlying pathophysiology of CINV continues to be elucidated; however, several central and peripheral sites involved in the process have been identified.[6,24] These regions include the following (**Figure II-2**):

- A loosely organized collection of receptor and effector nuclei located in the medulla is thought to interact to coordinate the emetic reflex.[6,22,24] This group of neurons is called the central pattern generator and has previously been referred to as the vomiting center (VC).[6]
- The chemoreceptor trigger zone (CTZ), also known as the area postrema, is located outside the blood-brain barrier at the caudal end of the fourth ventricle. It is susceptible to emetic substances in the blood or cerebral spinal fluid.[6] The CTZ has muscarinic acetylcholine receptor 1 (M_1), dopamine D_2 receptor (D_2), 5-HT_3, NK_1, and histamine-1 receptors, with 5-HT_3 and NK_1 receptors being associated with the activation of CTZ in CINV. The

CTZ does not independently initiate vomiting but works indirectly via neuronal projections sending impulses to the medulla.[25]

- Chemotherapy treatment damages rapidly dividing enterochromaffin cells located in the small intestine.[6] Enterochromaffin cells release 5-hydroxytryptamine/serotonin (5-HT), which binds to 5-HT_3 receptors on vagal afferent neurons. The vagal afferent neurons project to the dorsal vagal complex in the brain, which houses NK_1, 5-HT_3, and D_2 receptors. The efferent neurons from the dorsal vagal complex trigger the CTZ to elicit the vomiting reflex via the VC. The vagal afferent neurons may also stimulate vomiting directly via 5-HT_3 receptors located in the medulla and the CTZ.

Figure II-2. CINV Pathways and Drug Sites of Action[26]
(Adapted from Grunberg and Hesketh 1993)



5-HT_3 = serotonin subtype 3; CHEMO = chemotherapy; CINV = chemotherapy-induced nausea and vomiting; CTZ = chemoreceptor trigger zone; GI = gastrointestinal; NK_1 = neurokinin 1; VC = vomiting center

Several neurotransmitters, including dopamine, serotonin (5-HT), and substance P, are involved in stimulating emesis.[3] Drugs that block these neurotransmitters have been found to be effective in the prevention of CINV. Clinical studies with the early 5-HT_3 receptor antagonists (ie, ondansetron, granisetron, and dolasetron) indicated that serotonin plays a central role in the mechanism of acute CINV but a lesser role in delayed CINV.[3] The early 5-HT_3 receptor antagonists have much lower efficacy in delayed CINV compared to acute CINV.[27,28]

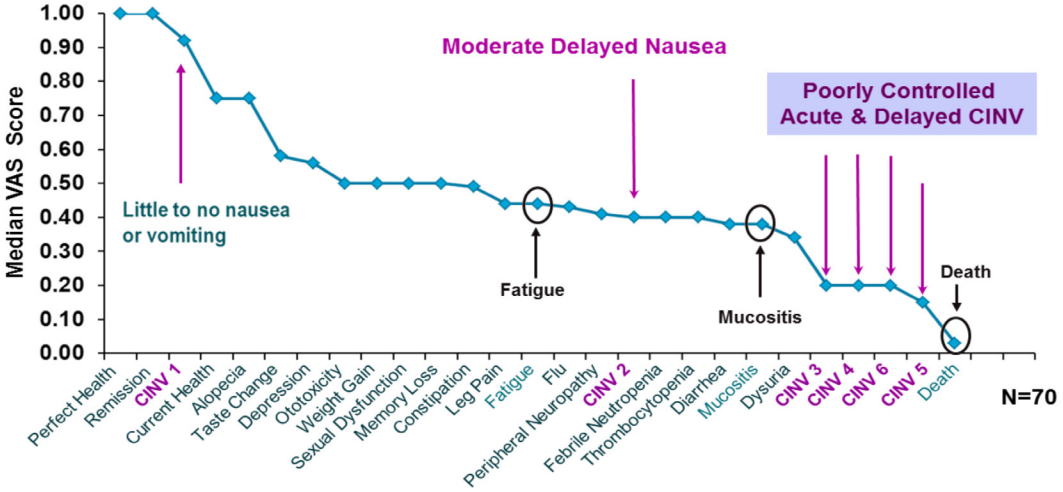
Delayed CINV appears to be mediated via the activation of NK_1 receptors by substance P.[2,3] In contrast to other 5-HT_3 receptor antagonists, palonosetron has demonstrated efficacy in preventing both acute and delayed CINV, which may be due to its ability to inhibit substance P–mediated responses via its interactions with the 5-HT_3 receptor. The combination of a 5-HT_3 receptor antagonist and a NK_1 receptor antagonist has been shown to provide better control of CINV over the 5 days after receiving HEC compared to treatment with a 5-HT_3 receptor antagonist alone.[29,30]

Societal, Humanistic, and Economic Impact

Inadequately controlled CINV can have significant clinical and economic consequences as well as an adverse impact on QOL. Clinical consequences, including dehydration, electrolyte disturbances, weight loss, and feeding-tube placement can lead to office visits, emergency room (ER) visits, and hospitalizations.[4-6] In addition, the effects of CINV can influence a patient's willingness or ability to comply with and successfully complete cancer treatment.

Among patients with a cancer diagnosis, CINV is one of the most distressing side effects of chemotherapy. Sun and colleagues[31] found that chemotherapy-experienced patients with ovarian cancer ranked severe CINV among their least favorable side effects of chemotherapy (**Figure II-3**).

Figure II-3. Chemotherapy-Experienced Patients' Rankings of Side Effects*† (2001 to 2004) (Adapted from Sun et al, 2005[31])



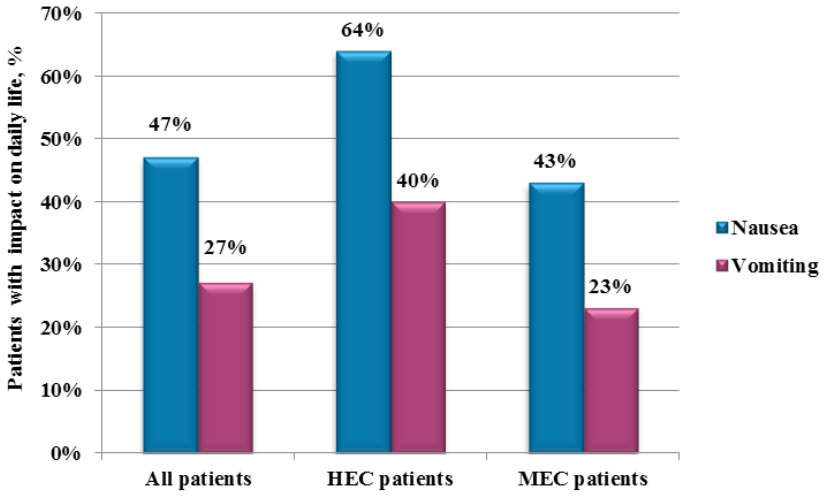
CINV = chemotherapy-induced nausea and vomiting; CINV 1 = days 1 to5 little to no nausea or vomiting; CINV 2 = day 1 complete control, days 2 to 5 moderate nausea, no vomiting; CINV 3 = day 1 complete control, days 2 to 5 moderate nausea, severe vomiting; CINV 4 = day 1 nausea and vomiting, days 2 to 5 moderate nausea; CINV 4 = day 1 nausea and vomiting, days 2 to 5 moderate nausea; CINV 5 = day 1 nausea and vomiting, days 2 to 5 moderate nausea, severe vomiting; CINV 6 = day 1 complete control, days 2 to 5 severe nausea VAS = visual analog scale

*The study was conducted in patients with ovarian cancer who had received at least 3 cycles of chemotherapy and were undergoing chemotherapy again for newly diagnosed or recurrent disease.

†Patient preference was measured by a modified VAS with scores ranging from 0 = least favorable to 1 = most favorable.

CINV impairs QOL and negatively impacts daily functioning of patients.[11,16,17] In a prospective study of US patients with cancer from 2007 to 2008, Haiderali and colleagues[11] found that 61.2% of patients experienced some form of CINV. Delayed CINV was more common than acute CINV (58.4% vs 34.3%, respectively), and nausea was experienced more frequently than vomiting (60.7% vs 16.9%). Reduced daily functioning was reported by 37.2% of all patients, and of those with poorly managed CINV, 90% reported a significant impact on daily functioning. In a separate study, delayed nausea was reported by 60.3% of patients receiving HEC and 52.4% of patients receiving MEC.[17] Overall, nausea had a greater impact on patients' daily functioning than vomiting (**Figure II-4**).

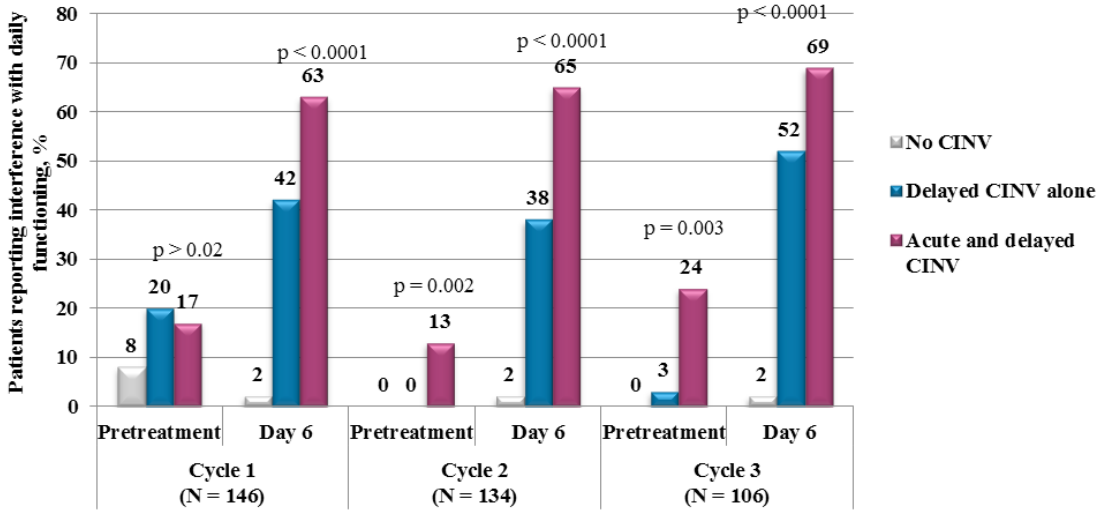
Figure II-4. Impact of Nausea and Vomiting on Patients' Daily Lives After HEC or MEC[17]



HEC = highly emetogenic chemotherapy; MEC = moderately emetogenic chemotherapy

An observational study evaluated the effect of CINV on daily functioning among patients scheduled to receive their first cycle of a new chemotherapy regimen.[16] During Cycles 1 to 3, acute and delayed nausea (experienced by up to 35% and 62% of patients, respectively) was a more significant problem than vomiting (up to 13% acute and 33% delayed). Both acute and delayed CINV had an impact on patients' daily functioning (**Figure II-5**).

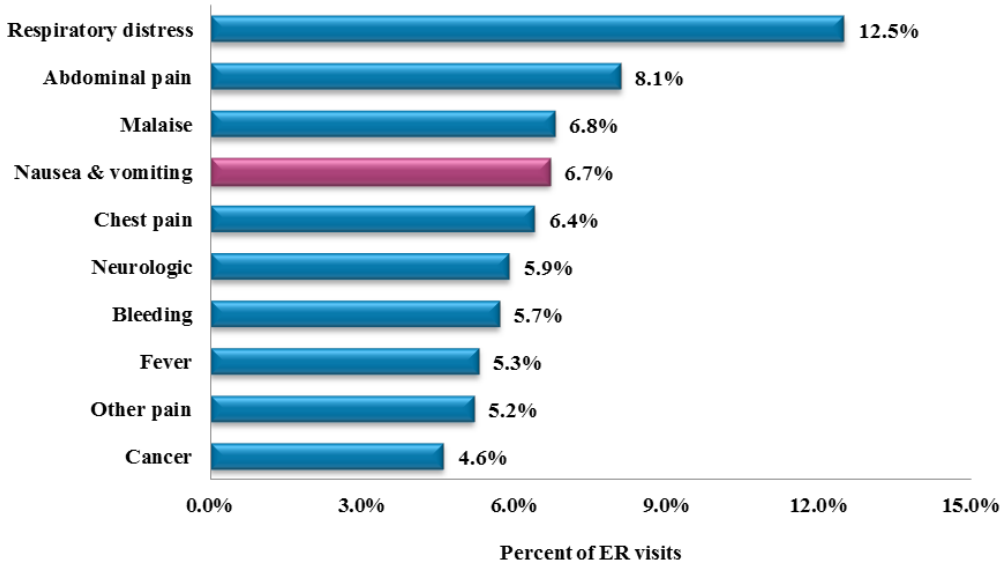
Figure II-5. Percentage of Patients Reporting Interference with Daily Functioning



CINV = chemotherapy-induced nausea and vomiting

Direct costs associated with managing CINV include the costs of antiemetic drugs, hospitalizations, and unscheduled physician and ER visits.[11] Mayer and colleagues[21] examined 37,760 ER visits for 27,644 patients with cancer and found that nausea and vomiting accounted for 6.7% of ER visits (**Figure II-6**).

Figure II-6. Chief Complaints for ER Visits in Patients Diagnosed with Cancer[21]



In a retrospective hospital outpatient database study from 2003 to 2007, Burke and colleagues[20] found that 14% of patients had a CINV-associated hospital visit. Inpatient admissions were the most common and most costly hospital visit, followed by outpatient and ER visits (64% vs 26% vs 10%, respectively; average cost per patient [2003 to 2007 US$]: $7448 vs $1494 vs $918, respectively). When averaged over all patients in the study, the mean hospital visit cost for CINV was $731. Haiderali and colleagues estimated that the average direct medical cost for patients with CINV

(including prescribed medications and physician-reported health care utilization) was $732 (2007 US$). On average, costs were greater for patients receiving HEC than for those receiving MEC ($819.16 vs $674.05, respectively; p = 0.11).[11]

Indirect costs associated with CINV include decreased work productivity and missed time from work for both patients and caregivers. Haiderali and colleagues reported that patients with severe CINV vs those with mild CINV were found to have greater indirect costs due to missed work ($379 vs $8) and lost productivity ($456 vs $86) (2007 US$).[11]

PRODUCT INFORMATION FOR AKYNZEO

Product Information Summary

AKYNZEO is a fixed-dose combination of netupitant and palonosetron 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 HEC.[1] Oral palonosetron prevents nausea and vomiting during the acute phase, and netupitant prevents nausea and vomiting during both the acute and delayed phases after cancer chemotherapy.

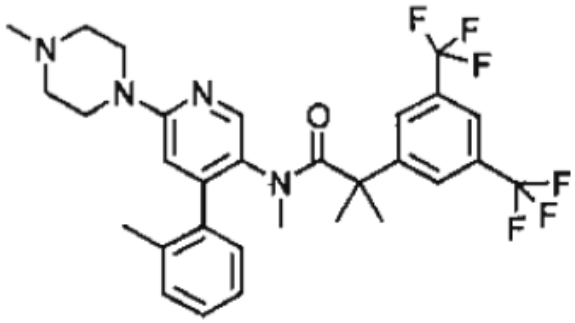
- Netupitant is a selective substance P/NK_1 receptor antagonist.
- Palonosetron is a 5-HT_3 receptor antagonist, structurally different from other 5-HT_3 receptor antagonists.
- Palonosetron and netupitant have been shown to exhibit additive and synergistic inhibitory effects on the substance P-mediated responses.
- The recommended dose in adults is one AKYNZEO capsule administered approximately one hour before the start of chemotherapy.
- Netupitant is a substrate and a moderate inhibitor of cytochrome P450 isoenzyme 3A4 (CYP3A4). AKYNZEO should be used with caution in patients receiving concomitant medications that are primarily metabolized via CYP3A4.

Generic, Brand, and Therapeutic Class

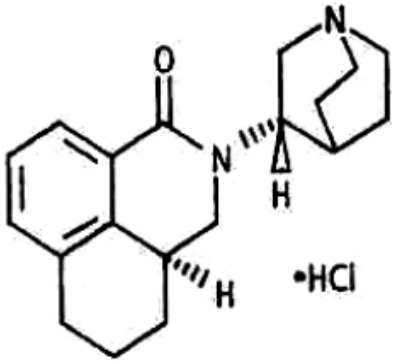
AKYNZEO is an oral fixed combination of netupitant, a substance P/NK_1 receptor antagonist, and palonosetron, a 5-HT_3 receptor antagonist.[1]

Figure II-7. Structural Formulas of Netupitant and Palonosetron[1]

Netupitant



Palonosetron HCl



National Drug Code, Dose, Dosage Form, Package Size, and Cost

Table II-5. Dosage Forms, Strengths, Package Sizes, NDC, and Costs

NDC[1]	Dose[1]	Dosage Form[1]	Package Size[1]	WAC
62856-796-01	300 mg netupitant/0.5 mg palonosetron	Capsule	One capsule	$476

NDC = National Drug Code; WAC = wholesale acquisition cost

American Hospital Formulary Service Classification[32]

The American Hospital Formulary Service (AHFS) classification for AKYNZEO is to be determined.

Indications[1]

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, HEC. 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.

Clinical Pharmacology

Please refer to the **AKYNZEO Prescribing Information—Clinical Pharmacology** section for complete information.

The combination of netupitant and palonosetron targets two critical pathways associated with acute and delayed CINV, the serotonin- and substance P-mediated pathways.[3,33]

Pharmacologic Properties of Netupitant

Netupitant is a selective antagonist of human substance P/NK_1 receptors.[1] Substance P is a tachykinin neuropeptide that functions as a neurotransmitter and mediates the induction of vomiting pathways by binding to the NK_1 receptor.[34] Delayed emesis has largely been associated with the activation of NK_1 receptors (broadly distributed in the central and peripheral nervous systems) by substance P.[1,2]

Netupitant has a high binding affinity for the NK_1 receptor, with a high degree of occupancy for a long duration. The receptor occupancy for the CINV dosing regimen of netupitant was measured in a human positron emission tomography study.[1,35] Netupitant was shown to cross the blood-brain barrier with a high occupancy of brain NK_1 receptors. NK_1 receptor occupancy in the striatum at 6, 24, 48, 72, and 96 hours after administration of 300 mg netupitant was 92.5%, 86.5%, 85.0%, 78.0%, and 76.0%, respectively. A 300-mg dose of netupitant is rapidly absorbed and has a long elimination half-life (**Table II-6**).

Table II-6. Half-Life of Netupitant and Other NK_1 Receptor Antagonists

	Netupitant[1]	Aprepitant and Fosaprepitant[36,37]
Half-life	80 ± 29 hours*	9 to 13 hours

*Mean ± standard deviation in patients with a diagnosis of cancer.

Pharmacologic Properties of Palonosetron

Palonosetron is a 5-HT_3 receptor antagonist with a strong binding affinity for this receptor and little or no affinity for other receptors.[1] Palonosetron is structurally different from other 5-HT_3 receptor antagonists (eg, ondansetron, granisetron, and dolasetron). Whereas the other 5-HT_3 receptor antagonists possess a two-ring indole moiety similar to the structure of serotonin, palonosetron is a tricyclic ring bound to a quinuclidine moiety (**Figure II-7**).[38,39] Compared to other 5-HT_3 receptor antagonists, palonosetron has a greater binding affinity and longer plasma half-life (**Table II-7**).[3] However, these attributes alone do not explain the clinical efficacy of palonosetron for both acute and delayed CINV vs the other 5-HT_3 receptor antagonists, which are effective for acute CINV only.

Table II-7. Binding Affinity and Half-Life of Oral Palonosetron vs Other Oral 5-HT_3 Receptor Antagonists

Characteristic	Palonosetron	Ondansetron	Granisetron
Half-life (oral dosage form)	48 ± 19 hours[1]*	3 to 5 hours[40]	6 hours[41]
Binding affinity (pKi)[42]	10.45	8.19	8.91

*Mean ± standard deviation in patients with a diagnosis of cancer.

As demonstrated in recent mechanistic studies, three other pharmacologic properties of palonosetron distinguish it from the other 5-HT_3 receptor antagonists, as follows:

- **Allosteric binding and positive cooperativity between palonosetron and 5-HT_3 receptors[39]**
  Allosteric binding (eg, binding at a different site than serotonin) induces a conformational change in the 5-HT_3 receptor, such that serotonin binding is inhibited indirectly.[43] Palonosetron binds to other portions of

the 5-HT_3 receptor as well as to the active site of the receptor; hence, the allosteric binding brings about an increased binding affinity between palonosetron and the 5-HT_3 receptor.[3]

- **Receptor internalization kinetics and prolonged inhibition of 5-HT_3 receptors[44]**
  Internalization of 5-HT_3 receptors would result in a decrease in receptors at the cell surface, leading to persistent inhibition of receptor function. Hence, receptor internalization is believed to account for the long-term inhibition by palonosetron of 5-HT_3 receptor function.
- **Inhibition of crosstalk between 5-HT_3 and NK_1 receptors[44]**
  Whereas palonosetron does not bind to the NK_1 receptor directly, it inhibits substance P-mediated responses via inhibition of receptor signaling crosstalk, which may help to explain palonosetron's efficacy in delayed CINV.

Pharmacologic Properties of AKYNZEO

In mechanistic studies, palonosetron and netupitant have been shown to exhibit an additive inhibitory effect on substance P-mediated responses. Stathis and colleagues[12] conducted an *in vitro* study using NG108-15 cells (known to express both 5-HT_3 and NK_1 receptors) to assess the inhibition of substance P-mediated response by netupitant and palonosetron. Results of the study showed that netupitant plus palonosetron exhibited a synergistic effect in the prevention of NK_1 receptor response against its endogenous agonist substance P, which may enhance the prevention of delayed emesis.

Thomas and colleagues[13] assessed the potential mechanism underlying the synergistic effect of netupitant and palonosetron by preincubabing NG108-15 cells with netupitant, palonosetron, or ondansetron. Results of several *in vitro* studies provide evidence that both netupitant (via direct binding) and palonosetron (through a 5-HT_3 receptor-mediated effect), but not ondansetron, can trigger NK_1 receptor internalization in NG108-15 cells. When netupitant and palonosetron are used together, the effect on receptor internalization is additive, and palonosetron-triggered NK_1 receptor internalization may require the presence of 5-HT_3 receptors. Consequently, the potential inhibition of downstream receptor crosstalk, in addition to direct receptor antagonism, represents an additional layer of inhibition that could trigger synergistic inhibitory effects.[12]

Noninferiority Study of Palonosetron IV and Oral Tablets

An oral formulation of palonosetron is included in AKYNZEO. The 0.5-mg palonosetron oral formulation is US Food and Drug Administration (FDA) approved; however, it is not marketed in the US.[45]

A single cycle, multicenter, multinational, randomized, double-blind, double-dummy, parallel-group, noninferiority study was conducted to assess the efficacy and safety of a single oral dose of palonosetron 0.50 mg vs a single IV dose of palonosetron 0.25 mg (each given with oral dexamethasone) for the prevention of nausea and vomiting in patients with cancer receiving HEC (N = 740).[1] The primary endpoint was complete response (CR) in the acute phase (0 to 24 hours). High response rates were observed in both treatment groups (88.9% vs 85.4% for oral palonosetron and IV palonosetron, respectively). Oral palonosetron was found to be noninferior to IV palonosetron (**Table II-8**). The incidence and severity of treatment-emergent AEs was similar between treatment groups.

Table II-8. Complete Response (FAS Population)

	Palonosetron Oral (n = 369)	Palonosetron IV (n = 369)
Responders, n (%)	328 (88.9)	315 (85.4)
95% CI	85.3, 91.7	81.4, 88.6
Difference in response rate, %	3.5	
95% CI	–1.3, 8.4	

CI = confidence interval; FAS = full analysis set; IV = intravenous
*Noninferiority margin set at 15%.

Contraindications[1]

None

Warnings and Precautions[1]

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

The development of serotonin syndrome has been reported with 5-HT_3 receptor antagonists. Most reports have been associated with the concomitant use of serotonergic drugs (eg, 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 antagonists 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 (eg, agitation, hallucinations, delirium, coma), autonomic instability (eg, tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (eg, tremor, rigidity, myoclonus, hyperreflexia, incoordination), and seizures, with or without gastrointestinal symptoms (eg, nausea, vomiting, diarrhea). Patients should be monitored for the emergence of serotonin syndrome, especially with concomitant use of AKYNZEO and other serotonergic drugs.

Adverse Reactions

Please refer to the **AKYNZEO Prescribing Information—Adverse Reactions** section for complete information.

In a single-cycle study of patients receiving cisplatin-based HEC, 136 patients were treated with AKYNZEO.[1] **Table II-9** shows adverse reactions reported at an incidence of ≥ 3% and for which the AKYNZEO rate exceeded that of palonosetron alone.

Table II-9. Adverse Reactions Occurring in ≥ 3% of Cancer Patients Receiving AKYNZEO and Cisplatin-Based HEC (Cycle 1)[1]

Adverse Reaction	AKYNZEO (n = 136)	Palonosetron 0.5 mg (n = 136)
Dyspepsia	4%	2%
Fatigue	4%	2%
Constipation	3%	1%
Erythema	3%	2%

In a study of patients receiving A/C-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.[1] **Table II-10** shows adverse reactions reported at an incidence of ≥ 3% and for which the AKYNZEO rate exceeded that of palonosetron alone during Cycle 1. The adverse reaction profile in subsequent cycles was similar to that observed in Cycle 1.

Table II-10. Adverse Reactions Occurring in ≥ 3% of Cancer Patients Receiving AKYNZEO and A/C-Based Chemotherapy (Cycle 1)[1]

Adverse Reactions	AKYNZEO (n = 752)	Palonosetron 0.5 mg (n = 725)
Headache	9%	7%
Asthenia	8%	7%
Fatigue	7%	5%

Drug Interactions[1]

Please refer to the **AKYNZEO Prescribing Information—Drug Interactions** section for complete information.

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 via CYP3A4. The plasma concentrations of CYP3A4 substrates can increase when coadministered with AKYNZEO. The inhibitory effect on CYP3A4 can last for multiple days.

A significant increase in the systemic exposure of dexamethasone was observed 4 days after a single dose of netupitant. The duration of the effect was not studied beyond 4 days. Administer a decreased dose of dexamethasone with AKYNZEO.

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.

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, paclitaxel, etoposide, irinotecan, cyclophosphamide, ifosfamide, imatinib, vinorelbine, vinblastine, and vincristine. Caution and monitoring for chemotherapeutic-related adverse reactions are advised in patients receiving chemotherapy agents metabolized primarily by CYP3A4.

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

Effects of Other Drugs on AKYNZEO

Netupitant, a component of AKYNZEO, is mainly metabolized by CYP3A4.

CYP3A4 Inducers
Avoid the concomitant use of AKYNZEO in patients who are chronically using a strong CYP3A4 inducer such as rifampin. A strong CYP3A4 inducer can decrease the efficacy of AKYNZEO by substantially reducing plasma concentrations of the netupitant component.

CYP3A4 Inhibitors
Concomitant use of AKYNZEO with a strong CYP3A4 inhibitor (eg, ketoconazole) can significantly increase systemic exposure to the netupitant component of AKYNZEO. However, no dosage adjustment is necessary for single-dose administration of AKYNZEO.

Serotonergic Drugs

Serotonin syndrome (including altered mental status, autonomic instability, and neuromuscular symptoms) has been described after the concomitant use of 5-HT_3 receptor antagonists and other serotonergic drugs, including SSRIs and SNRIs.

Dosing and Administration[1]

Please refer to the **AKYNZEO Prescribing Information—Dosing and Administration** section for complete information.

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 dexamethasone 8 mg orally once daily on Days 2 to 4.

Anthracycline and Cyclophosphamide 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.

Access

Please contact Eisai Medical Information at 1-888-274-2378 for more information regarding access.

Coprescribed/Concomitant Therapies

In clinical practice, antiemetic agents are commonly administered in combination regimens, given that antiemetics can work synergistically with each other, and no single antiemetic can currently be expected to provide complete protection from CINV.[4,22] AKYNZEO may be administered in combination with dexamethasone.

Comparison of 5-HT_3 Receptor Antagonists and NK_1 Receptor Antagonists for the Prevention of CINV

Comparisons of 5-HT_3 receptor antagonists and NK_1 receptor antagonists for the prevention of CINV are shown in **Tables II-11 and II-12**. Information found in the following tables is from the the full prescribing information of the respective products.

Table II-11. Comparison of 5-HT_3 Receptor Antagonists for the Prevention of CINV

	AKYNZEO® (netupitant/palonosetron) Capsules[1]	Aloxi® (palonosetron) Injection[38]	Ondansetron Injection[46] Zofran® (ondansetron) Tablets[40]* Zofran ODT® (ondansetron) Orally Disintegrating Tablets[40]* Zofran® (ondansetron) Oral Solution[40]* Zuplenz® (ondansetron) Oral Soluble Film[47]	Anzemet® (dolasetron mesylate) Tablets[48]	Granisetron Injection[49] Granisetron Tablets[41] Granisol® (granisetron) Oral Solution[50] Sancuso® (granisetron) Transdermal Patch[32]
Formulation(s)	Capsule for oral use	Injection for IV use	Injection for IV or IM use Tablets for oral use Orally disintegrating tablets (ODT) Solution for oral use Soluble film for oral use (Note: Ondansetron 32 mg IV injection is not indicated for the prevention of CINV.)	Tablets for oral use (Note: Anzemet IV injection is not indicated for the prevention of CINV.)	Injection for IV use Tablets for oral use Solution for oral use Patches for transdermal use
Half-life	Netupitant: 80 ± 29 hours Palonosetron: 48 ± 19 hours	40 hours	Injection: 3.5 hours (ages 19 to 40 years) 4.7 hours (ages 61 to 74 years) 5.5 hours (ages ≥ 75 years) Tablets, ODT, Oral Solution: 5.8 hours (female) 4.7 hours (male) Oral soluble film: 4.6 hours	7.9 hours (adults) 6.4 hours (adolescents)	Injection: 8.95 hours Tablets: 6.23 hours Oral solution: 6.23 hours Patch: Not reported
Indication for CINV	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, HEC.	• MEC: Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses • HEC: Prevention of acute nausa and vomiting associated with initial and repeat courses	Initial and repeat courses of emetogenic cancer chemotherapy	MEC: Prevention of nausea and vomiting associated with initial and repeat courses	• Prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer therapy including high-dose cisplatin • Up to 5 consecutive days (patch)
Additional FDA-approved indications	None	Prevention of postoperative nausea and vomiting	• Prevention of postoperative nausea and vomiting • Total body irradiation and fractionated abdominal radiation (tablets, ODT, oral solution, oral soluble film)	Prevention of postoperative nausea and vomiting	Total body irradiation and fractionated abdominal radiation (tablet, oral solution)

	AKYNZEO® (netupitant/palonosetron) Capsules[1]	Aloxi® (palonosetron) Injection[38]	Ondansetron Injection[46] Zofran® (ondansetron) Tablets[40]* Zofran ODT® (ondansetron) Orally Disintegrating Tablets[40]* Zofran® (ondansetron) Oral Solution[40]* Zuplenz® (ondansetron) Oral Soluble Film[47]	Anzemet® (dolasetron mesylate) Tablets[48]	Granisetron Injection[49] Granisetron Tablets[41] Granisol® (granisetron) Oral Solution[50] Sancuso® (granisetron) Transdermal Patch[32]
Recommended dosing for CINV in adults	HEC, including cisplatin-based chemotherapy: The recommended dosage in adults is one capsule 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. A/C-based chemotherapy and chemotherapy not considered highly emetogenic: The recommended dosage in adults is one capsule 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	0.25 mg IV administered over a period of 30 seconds, given 30 minutes before chemotherapy	• Injection: 0.15 mg/kg for three doses, up to a maximum of 16 mg per dose, infused over a period of 15 minutes–first dose beginning 30 minutes before chemotherapy, subsequent doses at 4 and 8 hours after the first ondansetron dose • Oral: Three 8-mg tablets or films orally 30 minutes before HEC, or one 8-mg tablet, ODT, or film, or 10 mL oral solution 30 minutes before MEC, then a second dose 8 hours after the first, and twice daily for 1 to 2 days after chemotherapy	100 mg given orally within 1 hour before chemotherapy	• Injection: 10 μg/kg administered IV within 30 minutes before chemotherapy, and only on the day of chemotherapy • Tablets: 2 mg up to 1 hour before chemotherapy, or 1 mg up to 1 hour before chemotherapy and 1 mg 12 hours after the first • Oral solution: 10 mL up to 1 hour before chemotherapy, or 5 mL up to 1 hour before chemotherapy and 5 mL 12 hours after the first • Patch: One 52-cm^2 patch a minimum of 24 hours before chemotherapy for up to 7 days
Effect on ECG interval(s) including QTc duration	Coadministration of single dose netupitant 600 mg and palonosetron 1.5 mg had no significant effects on the QTc interval	< 1% experienced QT prolongation	Ondansetron prolongs the QT interval in a dose-dependent manner. In addition, postmarketing cases of torsades de pointes have been reported in patients taking ondansetron. Avoid Zofran in patients with congenital long-QT syndrome. ECG monitoring is recommended for patients with electrolyte abnormalities (eg, hypokalemia or hypomagnesemia), congestive heart failure, or bradyarrhythmias, or patients taking other medicinal products that lead to QT prolongation.	QTc prolongation appears to be associated with hydrodolasetron concentration; the mean predicted increase in QTcF interval was 16.0 ms in renally impaired patients and 17.9 ms in elderly patients after a 100-mg oral dose. Exposure-dependent prolongations of PR and QRS intervals were also noted in healthy subjects.	Adequate QT assessment has not been conducted, but QT prolongation has been reported.

	AKYNZEO® (netupitant/palonosetron) Capsules[1]	Aloxi® (palonosetron) Injection[38]	Ondansetron Injection[46] Zofran® (ondansetron) Tablets[40]* Zofran ODT® (ondansetron) Orally Disintegrating Tablets[40]* Zofran® (ondansetron) Oral Solution[40]* Zuplenz® (ondansetron) Oral Soluble Film[47]	Anzemet® (dolasetron mesylate) Tablets[48]	Granisetron Injection[49] Granisetron Tablets[41] Granisol® (granisetron) Oral Solution[50] Sancuso® (granisetron) Transdermal Patch[32]
Contraindications	None	Known hypersensitivity to the drug or any of its components.	• Known hypersensitivity to the drug • Concomitant use of apomorphine with ondansetron is contraindicated.	Known hypersensitivity to the drug	Known hypersensitivity to the drug or any of its components
Warnings†	• Hypersensitivity reactions have been reported in patients receiving IV palonosetron with or without known hypersensitivity to other 5-HT_3 receptor antagonists. • Serotonin syndrome has been reported with 5-HT_3 receptor antagonists alone but particularly with concomitant use of serotonergic drugs.	• Hypersensitivity reactions, including anaphylaxis, have been reported with or without known hypersensitivity to other 5-HT_3 receptor antagonists. • Serotonin syndrome has been reported with 5-HT_3 receptor antagonists alone but particularly with concomitant use of serotonergic drugs	• Hypersensitivity reactions, including anaphylaxis and bronchospasm, have been reported in patients who have exhibited hypersensitivity to other selective 5-HT_3 receptor antagonists. • QT prolongation occurs in a dose-dependent manner. Cases of torsades de pointes have been reported. Avoid Zofran in patients with congenital long-QT syndrome. • The development of serotonin syndrome has been reported with 5-HT_3 receptor antagonists alone. Most reports have been associated with concomitant use of serotonergic drugs.	• QT interval prolongation; torsades de pointes reported postmarketing; avoid in patients with congenital long-QT syndrome, hypomagnesemia, or hypokalemia; PR and QRS interval prolongation and reports of second- or third-degree AV block, cardiac arrest, and ventricular arrhythmias • 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.	• Do not use instead of nasogastric suction; may mask a progressive ileus and/or gastric distention • May cause application-site reactions (patch); may be affected by direct sunlight (patch) • 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.
Most common AEs	Most common adverse reactions (incidence ≥ 3% and greater than palonosetron) are headache, asthenia, dyspepsia, fatigue, constipation, and erythema.	Headache (9%), constipation (5%), diarrhea (1%), dizziness (1%)	Injection (three 0.15-mg/kg doses): headache (17%), diarrhea (16%), fever (8%) Oral (single 24-mg dose): headache (11%), diarrhea (4%) Oral (3 days of therapy): headache (24%), fatigue (13%), constipation (9%), diarrhea (6%)	25-mg dose: headache (17.9%), fatigue (2.6%), diarrhea (2.1%), bradycardia (5.1%) 100-mg dose: headache (23%), fatigue (6%), diarrhea (5%), bradycardia (4%)	Headache (14% to 21%), constipation (3% to 18%); additional AEs were asthenia, somnolence, and diarrhea (injection, tablets, oral solution) Constipation (5.4%) and headache (0.7%) (patch)

	AKYNZEO® (netupitant/palonosetron) Capsules[1]	Aloxi® (palonosetron) Injection[38]	Ondansetron Injection[46] Zofran® (ondansetron) Tablets[40]* Zofran ODT® (ondansetron) Orally Disintegrating Tablets[40]* Zofran® (ondansetron) Oral Solution[40]* Zuplenz® (ondansetron) Oral Soluble Film[47]	Anzemet® (dolasetron mesylate) Tablets[48]	Granisetron Injection[49] Granisetron Tablets[41] Granisol® (granisetron) Oral Solution[50] Sancuso® (granisetron) Transdermal Patch[32]
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 CYP3A4 Inducers (eg, rifampin): Decreased plasma concentrations of netupitant; avoid use 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 SSRIs and SNRIs	Low potential for clinically significant drug interactions	CYP3A4, CYP2D6, CYP1A2 substrate, without induction or inhibition; drugs that induce or inhibit these enzymes may affect clearance, but limited data does not show dosage adjustment is necessary; do not administer with apomorphine due to profound hypotension or loss of consciousness.	Avoid with diuretics; may induce electrolyte abnormalities; antiarrhythmic drugs; QT-prolonging drugs; cumulative high-dose anthracycline therapy; caution with drugs that prolong any ECG interval and/or cause hypokalemia or hypomagnesemia	No definitive studies have been conducted, but no induction or inhibition of CYP enzymes occurs. Clinical significance of interactions with ketoconazole and phenobarbital are unknown.

5-HT_3 = serotonin subtype 3; A/C = anthracycline/cyclophosphamide; AE = adverse event; AV = atrioventricular; CINV = chemotherapy-induced nausea and vomiting; CYP = cytochrome P450; ECG = electrocardiogram; FDA = US Food and Drug Administration; HEC = highly emetogenic chemotherapy; IM = intramuscular; IV = intravenous; MEC = moderately emetogenic chemotherapy; ms = millisecond; ODT = orally disintegrating tablet; QTc = corrected QT interval; QTcF = Fridericia-corrected QT interval; SNRIs = serotonin norepinephrine reuptake inhibitors; SSRIs = selective serotonin reuptake inhibitors

*Generic ondansetron oral tablets, orally disintegrating tablets, and oral solution available

Table II-12. Comparison of NK1 Receptor Antagonists for the Prevention of CINV

	AKYNZEO® (netupitant/palonosetron) Capsules[1]	Emend® (aprepitant) Capsules[36]	Emend® (fosaprepitant dimeglumine) Injection[37]
Formulation(s)	Capsule, for oral use	Capsules, for oral use	Injection, for IV use
Half-life	Netupitant: 80 ± 29 hours Palonosetron: 48 ± 19 hours	9 to 13 hours	9 to 13 hours
Indication for CINV	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, HEC.	In combination with other antiemetic agents: • Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of HEC including high-dose cisplatin • Prevention of nausea and vomiting associated with initial and repeat courses of MEC	In combination with other antiemetic agents: • Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of HEC including high-dose cisplatin • Prevention of nausea and vomiting associated with initial and repeat courses of MEC
Additional FDA-approved indications	None	Prevention of postoperative nausea and vomiting	None
Recommended dosing for CINV	HEC, including cisplatin-based chemotherapy: The recommended dosage in adults is one capsule 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. A/C-based chemotherapy and chemotherapy not considered highly emetogenic: The recommended dosage in adults is one capsule 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	125 mg orally 1 hour before chemotherapy (Day 1) and 80 mg orally once daily in the morning on Days 2 and 3	Prevention of CINV after HEC: • 150 mg IV on Day 1 only as an infusion over a period of 20 to 30 minutes initiated approximately 30 minutes before chemotherapy Or • 115 mg IV on Day 1 as an infusion over a period of 15 minutes initiated 30 minutes before chemotherapy followed by aprepitant 80 mg orally on Days 2 and 3 Prevention of CINV following MEC: • 115 mg IV on Day 1 only as an infusion over a period of of 15 minutes initiated 30 minutes before chemotherapy followed by aprepitant 80 mg orally on Days 2 and 3
Effect on ECG interval(s) including QTc duration	Coadministration of single-dose netupitant 600 mg and palonosetron 1.5 mg had no significant effect on the QTc interval.	No effect	No effect
Contraindications	None	• Hypersensitivity to any component of this medication. • Should not be used concurrently with pimozide, terfenadine, astemizole, or cisapride because inhibition of CYP3A4 could result in elevated plasma concentrations of these drugs, potentially causing serious or life-threatening reactions.	• Hypersensitivity to any component of this medication. • Should not be used concurrently with pimozide, terfenadine, astemizole, or cisapride because inhibition of CYP3A4 could result in elevated plasma concentrations of these drugs, potentially causing serious or life-threatening reactions.

	AKYNZEO® (netupitant/palonosetron) Capsules[1]	Emend® (aprepitant) Capsules[36]	Emend® (fosaprepitant dimeglumine) Injection[37]
Warnings	• Hypersensitivity reactions have been reported in patients receiving IV palonosetron with or without known hypersensitivity to other 5-HT_3 receptor antagonists. • Serotonin syndrome has been reported with 5-HT_3 receptor antagonists alone but particularly with concomitant use of serotonergic drugs.	• Coadministration with warfarin may result in a clinically significant decrease in the INR of prothrombin time. • The efficacy of hormonal contraceptives during and for 28 days after the last dose of Emend may be reduced. • Use with caution in patients receiving concomitant medications that are primarily metabolized via CYP3A4. • Caution should be exercised when administered to patients with severe hepatic impairment.	• Use with caution in patients receiving concomitant medications that are primarily metabolized via CYP3A4. • Isolated reports of immediate hypersensitivity reactions including flushing, erythema, dyspnea, and anaphylaxis have occurred during infusion of fosaprepitant. • Coadministration with warfarin may result in a clinically significant decrease in the INR of prothrombin time. • The efficacy of hormonal contraceptives during and for 28 days after the last dose of fosaprepitant may be reduced.
Most common AEs	Most common adverse reactions (incidence ≥ 3% and greater than palonosetron) are headache, asthenia, dyspepsia, fatigue, constipation, and erythema.	AEs with incidence > 10%: alopecia, anorexia, asthenia/fatigue, constipation, diarrhea, headache, hiccups, nausea	Similar to aprepitant, with the addition of infusion site reactions (3%)
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 • CYP3A4 Inducers (eg, rifampin): Decreased plasma concentrations of netupitant; avoid use • Serotonin syndrome (including altered mental status, autonomic instability, and neuromuscular symptoms) has been described following the concomitant use of 5-HT3 receptor antagonists and other serotonergic drugs, including SSRIs and SNRIs	• CYP3A4 substrate: Coadministration with drugs that inhibit or induce CYP3A4 activity may result in increased or reduced plasma concentrations of aprepitant, respectively. • CYP2C9 inducer: Coadministration with drugs that are metabolized via CYP2C9 (eg, warfarin, tolbutamide), may result in lower plasma concentrations of these drugs. • Oral dexamethasone doses should be decreased by approximately 50% when coadministered with Emend (125-mg/80-mg regimen) • Aprepitant may reduce the efficacy of hormonal contraceptives during and for 28 days after administration of the last dose of aprepitant.	• CYP3A4 substrate: Coadministration with drugs that inhibit or induce CYP3A4 activity may result in increased or reduced plasma concentrations of fosaprepit ant, respectively. • CYP2C9 inducer: Coadministration with drugs that are metabolized via CYP2C9 (eg, warfarin, tolbutamide) may result in lower plasma concentrations of these drugs. • Oral dexamethasone dose should be decreased by approximately 50% when coadministered with fosaprepitant 150 mg or 115 mg. • Fosaprepitant may reduce the efficacy of hormonal contraceptives during and for 28 days after administration of the last dose of fosaprepitant.

5-HT_3 = serotonin subtype 3; AE = adverse event; CINV = chemotherapy-induced nausea and vomiting; CYP = cytochrome P450; ECG = electrocardiogram; FDA = US Food and Drug Administration; HEC = highly emetogenic chemotherapy; INR = International Normalized Ratio; IV = intravenous; MEC = moderately emetogenic chemotherapy; NK_1 = neurokinin 1; QTc = corrected QT interval; SNRIs = serotonin norepinephrine reuptake inhibitors; SSRIs = selective serotonin reuptake inhibitors

PLACE OF AKYNZEO IN THERAPY

Approach to Prevention of CINV

Prevention of CINV is an important component of supportive care for patients receiving cytotoxic chemotherapy. The goal of antiemetic therapy is to prevent nausea and/or vomiting throughout the entire period of risk, which may extend to 3 or more days after administration of HEC.[4,6] The choice of antiemetic regimen is based primarily on the emetogenic potential of the chemotherapy agent/agents and the risk of delayed CINV.

The currently available antiemetic agents target specific neurotransmitters in key pathways involved in stimulating emesis (**Table II-13**).

Table II-13. Guideline-Recommended Antiemetic Agents Used in the Prevention of CINV After HEC or MEC[4,8,9]

5-HT_3 Receptor Antagonists
Dolasetron
Granisetron
Ondansetron
Palonosetron
NK_1 Receptor Antagonists
Aprepitant
Fosaprepitant
Corticosteroids
Dexamethasone
Dopamine/5-HT_2 Receptor Antagonists
Olanzapine*

5-HT_3 = serotonin subtype 3; CINV = chemotherapy-induced nausea and vomiting; HEC = highly emetogenic chemotherapy; MEC = moderately emetogenic chemotherapy; NCCN = National Comprehensive Cancer Network; NK_1 = neurokinin 1
*Included in NCCN Guidelines only

By targeting different neuronal pathways, antiemetic agents exert their effects at different phases during the course of CINV. No single antiemetic agent has been shown to provide complete protection in all phases of CINV; therefore, agents with different mechanisms of action are typically used in combination.[4,8,9] Antiemetic therapy is initiated before the administration of chemotherapy and can be continued throughout the period when delayed emesis may occur.[4] The period of risk for CINV lasts at least 3 days after administration of HEC and at least 2 days after MEC.

Histamine receptor blockers or proton pump inhibitors are also included as adjuncts to antiemetic regimens to prevent dyspepsia, which can mimic nausea.[4] Benzodiazepines, such as lorazepam, are often used to treat anxiety and decrease the risk of anticipatory emesis.[6] In addition, dietary modifications, such as eating small frequent meals and making healthful food choices may aid in alleviating the symptoms of CINV.[4]

Guidelines for the Management of CINV

Evidence-based treatment guidelines for the prevention and management of CINV have been developed by the NCCN,[4] the American Society of Clinical Oncology (ASCO),[8] and the Multinational Association of Supportive Care in Cancer (MASCC) and European Society for Medical Oncology (ESMO).[9] Many of the recommendations and strategies for the prevention of acute and delayed CINV provided by these organizations are in close agreement with each other (**Table II-14**).

- For the *prevention of CINV post-HEC*, triple therapy with a 5-HT_3 receptor antagonist, dexamethasone, and a NK_1 receptor antagonist is recommended.[4,8,9] NCCN guidelines recommend palonosetron as the preferred 5-HT_3 receptor antagonist for the prevention of acute and delayed emesis associated with HEC.[4]
- For the *prevention of CINV post-MEC*, a 5-HT_3 receptor antagonist and dexamethasone is recommended, with a NK_1 receptor antagonist being an optional addition to the regimen for selected patients, as appropriate.[4,8,9] The NCCN, ASCO, and MASCC/ESMO guidelines all recommend palonosetron as the preferred 5-HT_3 receptor antagonist for the prevention of emesis associated with MEC.

For patients receiving *multiday chemotherapy*, the standard of care is prophylactic treatment with a 5-HT_3 receptor antagonist plus dexamethasone.[4] An NK_1 receptor antagonist can be added if the multiday chemotherapy regimen is highly emetogenic and is associated with significant delayed CINV. Per NCCN guidelines, palonosetron may also be used before the start of Day 3 of chemotherapy, instead of multiple oral or IV daily doses of other 5-HT_3 receptor antagonists.[4]

Table II-14. Evidence-Based Guidelines for the Prevention of CINV

Category	2014 NCCN*[4]	2011 ASCO[8]	2013 MASCC /ESMO[9]
Highly Emetogenic Chemotherapy (HEC) Antiemetic Regimen	**NK_1 RA-containing regimen** • 5-HT_3 RA (*Day 1*): – Palonosetron (preferred) or – Other 5-HT_3 RA • Steroid (*Days 1 to 4*) – Dexamethasone • NK_1 RA – Aprepitant (*Days 1 to 3)* – Fosaprepitant *(Day 1)* Or **Olanzapine-containing regimen** • Olanzapine (*Days 1 to 4*) • Palonosetron (*Day 1*) • Dexamethasone (*Day 1*) **± Adjunctive drugs (for both regimens)** • Lorazepam *(Days 1 to 4)* • H_2 blocker or PPI	5-HT_3 RA *(Day 1)* Steroid *(Days 1 to 3 or Days 1 to 4)* • Dexamethasone NK_1 RA • Fosaprepitant *(Day 1)* or • Aprepitant *(Days 1 to 3)* ± Adjunctive drugs • Lorazepam or • Diphenhydramine	5-HT_3 RA (*Day 1*) Steroid (*Days 1 to 4*) • Dexamethasone NK_1 RA • Fosaprepitant (*Day 1*) or • Aprepitant (*Days 1 to 3*)
Anthracycline and Cyclophosphamide (A/C) Regimen	Same as HEC	Same as HEC	5-HT_3 RA *(Day 1)* • If the NK_1 RA is not available, palonosetron is the preferred 5-HT_3 RA. Steroid (*Day 1*) • Dexamethasone NK_1 RA • Fosaprepitant *(Day 1)* or • Aprepitant *(Days 1 to 3)*

Category	2014 NCCN*[4]	2011 ASCO[8]	2013 MASCC /ESMO[9]
Moderately Emetogenic Chemotherapy (MEC) Antiemetic Regimen	*Day 1* **5-HT_3 RA + steroid ± NK_1 RA regimen** • 5-HT_3 RA – Palonosetron (preferred) • Steroid – Dexamethasone • With or without NK_1 RA – Aprepitant – Fosaprepitant Or **Olanzapine-containing regimen** • Olanzapine • Palonosetron • Dexamethasone **± Adjunctive drugs (for both regimens)** • Lorazepam • H_2 blocker or PPI *Days 2–3:* **5-HT_3 RA monotherapy (unless palonosetron used on Day 1)** Or **Steroid monotherapy** • Dexamethasone Or **NK_1 RA ± steroid** • Aprepitant (if NK_1 RA was used on Day 1) Or **Olanzapine on Days 2 to 4 (if given Day 1)** **± Adjunctive drugs *(with all regimens)*** • Lorazepam • H_2 blocker or PPI	5-HT_3 RA *(Day 1)* • Palonosetron (preferred) Steroid *(Days 1 to 3)* • Dexamethasone ± NK_1 RA *(Day 1)* • Aprepitant ± Adjunctive drugs • Lorazepam or • Diphenhydramine	5-HT_3 RA *(Day 1)* • Palonosetron (preferred) Steroid (*Days 1 to 3*) • Dexamethasone

5-HT_3 RA = serotonin subtype 3 receptor antagonist; ASCO = American Society of Clinical Oncology; CINV = chemotherapy-induced nausea and vomiting; ESMO = European Society for Medical Oncology; H_2 = histamine H_2 receptor; MASCC = Multinational Association of Supportive Care in Cancer; NCCN = National Comprehensive Cancer Network; NK_1 RA = neurokinin 1 receptor antagonist; PPI = proton pump inhibitor
*Please refer to www.NCCN.org for complete information.

Unmet Needs in the Prevention of CINV

Despite the availability of numerous prophylactic antiemetic medications and published guidelines for their use, the prevention of CINV remains a challenge. As described above, the incidence and severity of CINV, particularly delayed nausea and vomiting, are frequently underestimated by physicians and nurses.[10] In addition, there is evidence that adherence to guidelines for CINV prophylaxis is suboptimal in clinical practice. Gomez and colleagues reported unexpectedly low adherence rates to guideline recommendations for antiemetic therapy among patients with lung cancer receiving HEC or MEC.[5] During the period 2001 to 2007, 5-HT_3 antagonists with dexamethasone were taken by approximately 60% to 90% of patients receiving HEC or MEC. However, adherence to guideline recommendations for

NK_1 receptor antagonists was substantially lower, at < 10%. Furthermore, whereas the prevention of CINV has improved substantially over the past years, some patients continue to experience CINV, and control of nausea is a particular challenge. In an observational study of CINV among patients with cancer, 61.2% of patients experienced some form of CINV.[11] Prophylactic antiemetic therapy was provided; however, prescribed regimens and compliance varied broadly. Nausea was reported much more frequently than vomiting among both HEC and MEC recipients (**Table II-15**).

Table II-15. Prevalence of CINV[11]

n (%)	MEC (n = 125)	HEC (n = 53)
Acute CINV	46 (37)	15 (28)
Delayed CINV	69 (55)	35 (66)
Total CINV	74 (59)	35 (66)
Nausea	74 (59)	34 (64)
Vomiting	17 (14)	13 (25)

CINV = chemotherapy-induced nausea and vomiting; HEC = highly emetogenic chemotherapy; MEC = moderately emetogenic chemotherapy

There is an unmet need for improved prevention of delayed CINV, particularly nausea. In addition, there is a need for improved adherence to guideline-based antiemetic therapy.

AKYNZEO for the Prevention of CINV

AKYNZEO is a fixed-dose combination of netupitant, a highly selective NK_1 receptor antagonist, and palonosetron, a 5-HT_3 receptor antagonist with strong binding affinity, 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 HEC. Palonosetron prevents nausea and vomiting during the acute phase, and netupitant prevents nausea and vomiting during the acute and delayed phases after cancer chemotherapy.[1] AKYNZEO combines two antiemetic medications, targeting two key pathways associated with CINV into a single oral dosage form. This combination may provide convenience for both patients and prescribers.

AKYNZEO has demonstrated efficacy in the prevention of acute and delayed CINV after treatment with HEC or A/C regimens.

- After treatment with HEC or A/C chemotherapy, CR rates (defined as no emesis and no rescue medication use) were significantly greater in the AKYNZEO group compared to the oral palonosetron group (both in combination with dexamethasone) (**Table II-16**).

Table II-16. Cycle 1 Overall Complete Response Rates

Study	Complete Response Rate		p value
	AKYNZEO + Dex	Oral Palonosetron + Dex	
NEPA 07-07[51] HEC Study	89.6% (n = 135)	76.5% (n = 136)	0.004
NEPA 08-18[15] A/C Study	74.3% (n = 724)	66.6% (n = 725)	0.001

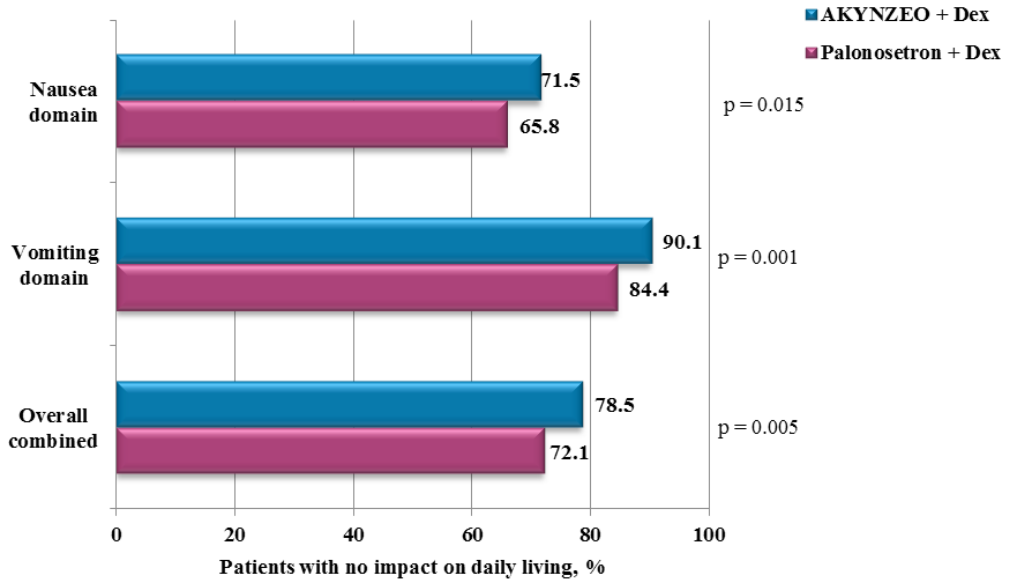
A/C = anthracycline/cyclophosphamide; Dex = dexamethasone; HEC = highly emetogenic chemotherapy

- After treatment with HEC, significantly more patients treated with AKYNZEO vs palonosetron achieved no significant nausea and complete protection (CP; defined as no emesis, no rescue medication use, and no significant nausea) during the acute, delayed, and overall phases ($p \leq 0.05$).[51]
- Among patients receiving A/C, significantly more of those treated with AKYNZEO vs palonosetron achieved no significant nausea and CP during the delayed and overall phases ($p < 0.05$).[52]

AKYNZEO improves daily functioning and QOL for patients receiving HEC and A/C.

- In a clinical trial, a greater proportion of AKYNZEO-treated patients reported no impact on daily living (NIDL) with respect to nausea, vomiting, and combined domains compared to palonosetron-treated patients (**Figure II-8**).[15]

Figure II-8. Proportion of Patients With No Impact on Daily Living After A/C: Overall Phase[52]



A/C = anthracycline/cyclophosphamide; Dex = dexamethasone

The antiemetic efficacy of AKYNZEO is maintained over repeated cycles of HEC and A/C.

- A multiple cycle extension study of NEPA 08-18 enrolled 1286 patients.[52] Patients received the same treatment as assigned in Cycle 1. Across all cycles, CR rates for the overall phase were significantly greater in the AKYNZEO group compared to the palonosetron group ($p = 0.001$ for Cycle 1; $p < 0.0001$ for Cycles 2 to 4). AE rates across multiple cycles were similar between the two treatment groups.
- Among patients treated with AKYNZEO in the NEPA 10-29 study, CR rates during the overall phase after MEC or HEC were high (ranging from 81% to 92%) across 6 cycles chemotherapy.[18]

In clinical trials, the overall incidence, type, frequency, and intensity of treatment-emergent AEs were comparable between patients treated with AKYNZEO and those treated with palonosetron.[15,51]

- In clinical trials, the majority of AEs among patients treated with AKYNZEO were mild or moderate in intensity.[15,51] The most common AKYNZEO-related AEs among patients receiving A/C were headache and constipation.[15] After treatment with HEC, the most common AKYNZEO-related AEs were hiccups and headache.[51]
- AKYNZEO was studied in over > 1400 chemotherapy cycles, with more than 75% of patients receiving up to 4 chemotherapy cycles.[18] The safety profile of AKYNZEO was similar to that of aprepitant + palonosetron. The most frequent AKYNZEO-related AEs included constipation (3.6%) and headache (1.0%); there was no indication of increasing AEs over multiple cycles.[18]

SECTION III:
Supporting Clinical Evidence for AKYNZEO®
(netupitant/palonosetron) Capsules

SUPPORTING CLINICAL EVIDENCE FOR AKYNZEO

This section of the dossier will provide detailed summaries of one Phase II trial and two Phase III trials for AKYNZEO as well as brief summaries in the **AKYNZEO Supporting Clinical Evidence Table** (**Table III-11**). Information on clinical trials of AKYNZEO can be found in the clinical trials registry, www.clinicaltrials.gov.

Summary of Phase II and Phase III Pivotal Trials for AKYNZEO

The evidence for the efficacy and safety of AKYNZEO in preventing CINV in patients receiving MEC, A/C chemotherapy or HEC is provided in one Phase II and two Phase III trials. All of these trials were double-blind, randomized, double-dummy, multicenter, parallel-group studies of AKYNZEO (netupitant 300 mg/palonosetron 0.5 mg) (FDA-approved dose) given as a single oral dose 60 minutes before administration of chemotherapy. The efficacy endpoints and safety assessments evaluated in these Phase II and III trials are summarized in **Table III-1**.

Table III-1. Efficacy Endpoints and Safety Assessments
Studies NEPA 07-07, NEPA 08-18, and NEPA 10-29

	NEPA 07-07 Dose-Finding Phase II Study Single Cycle of Cisplatin-Based HEC	NEPA 08-18 Phase III Study Single Cycle of A/C (Patients had the option to receive multiple cycles)	NEPA 10-29 Phase III Study Multiple Cycles of HEC or MEC
Primary endpoint	CR during the overall phase period	CR during the delayed phase	Safety
Secondary endpoints	• CR during the following time periods after chemotherapy administration: – Acute phase – Delayed phase • CP during the acute, delayed, and overall phases • No emesis during the acute, delayed, and overall phases • No significant nausea during the acute, delayed, and overall phases*	• CR during the acute phase • CR during the overall phase • CP during the acute, delayed, and overall phases • No emesis during the acute, delayed, and overall phases • No significant nausea during the acute, delayed, and overall phases • Functional Living Index- Emesis (FLIE) questionnaire (proportion of patients with scores reflecting "no impact on daily life")	• CR during the acute, delayed, and overall phases • No significant nausea during the acute, delayed, and overall phases
Safety assessments	• AEs • Vital sign measurements • Laboratory tests • Physical examination • ECG recordings	• AEs • Vital sign measurements • Laboratory tests • Physical examination • ECG recordings	• AEs • Vital sign measurements • Laboratory tests including cardiac troponin (CTnI) levels • Physical examination • ECG recordings including LVEF

A/C = anthracycline/cyclophosphamide; AE = adverse event; CP = complete protection (defined as no emetic episode, no need for rescue medication, and no significant nausea); CR = complete response (defined as no emetic episode, no need for rescue medication); ECG = electrocardiogram; HEC = highly emetogenic chemotherapy; LVEF = left ventricular ejection fraction; MEC = moderately emetogenic chemotherapy; NEPA = netupitant/palonosetron; VAS = visual analog scale
*Significant nausea was defined as < 25 mm on the 100-mm VAS scale (0 = "no nausea" and 100 = "nausea as bad as it can be").

AKYNZEO for the Prevention of CINV After HEC
Study NEPA 07-07
Hesketh et al, 2014[51]

Key Findings

This was a Phase II, randomized, double-blind, dose-finding, multicenter study comparing the efficacy and tolerability of single oral doses of netupitant 100 mg, 200 mg, or 300 mg combined with oral palonosetron 0.5 mg vs oral palonosetron 0.5 mg alone in preventing CINV after HEC (N = 694).

Primary Endpoint

- Significantly more patients receiving netupitant/palonosetron vs palonosetron alone had a CR during the overall phase (netupitant 100 mg, 87.4% [p = 0.018]; netupitant 200 mg, 87.6% [p = 0.017]; netupitant 300 mg, 89.6% [p = 0.004]; palonosetron alone, 76.5%) (**Figure III-2**).

Secondary Endpoints

- During the acute phase, more patients receiving netupitant 300 mg vs palonosetron alone experienced a CR (98.5% vs 89.7%; $p \leq 0.01$), and during the delayed phase, more patients receiving netupitant 100 mg (90.4%; $p \leq 0.05$), netupitant 200 mg (91.2%; $p \leq 0.01$), and netupitant 300 mg (90.4%; $p \leq 0.05$) vs palonosetron alone (80.1%) experienced a CR.
- Significantly more patients in the netupitant 300 mg group reported no emesis during the acute, delayed, and overall phases compared to the palonosetron alone group (all p values ≤ 0.01).
- CP was reported by more patients who received netupitant 300 mg vs palonosetron alone during the acute, delayed, and overall phases ($p \leq 0.01$, $p \leq 0.05$, and $p \leq 0.01$, respectively).
- ***Safety***
- The most common treatment-emergent, drug-related AEs reported in all treatment groups were hiccups (netupitant 100 mg, 3.7%; netupitant 200 mg, 3.6%; netupitant 300 mg, 5.1%; palonosetron alone, 3.7%) and headache (netupitant 100 mg, 0.7%; netupitant 200 mg, 2.2%; netupitant 300 mg, 0.7%; palonosetron alone, 1.5%).
- The treatment groups had comparable rates of patients who developed treatment-emergent electrocardiogram (ECG) abnormalities.

Objective: To compare the efficacy and tolerability of single oral doses of netupitant (100 mg, 200 mg, or 300 mg) combined with oral palonosetron 0.5 mg vs oral palonosetron 0.5 mg alone in preventing CINV after HEC in patients naïve to chemotherapy.

Patients and Methods: This was a Phase II, multicenter, randomized, double-blind, double-dummy, parallel-group, dose-finding study conducted in 44 sites in Russia and Ukraine. Patients were randomized in a 1:1:1:1 ratio to receive a single oral dose of one of the following four treatment arms and one exploratory arm:

- Netupitant 100 mg plus palonosetron 0.5 mg
- Netupitant 200 mg plus palonosetron 0.5 mg
- Netupitant 300 mg plus palonosetron 0.5 mg
- Oral palonosetron 0.5 mg

In a fifth, exploratory arm of the study, patients received oral aprepitant 125 mg plus IV ondansetron 32 mg on Day 1 followed by aprepitant 80 mg on Days 2 to 3. Corticosteroid treatment with dexamethasone was included in all groups; the dose of dexamethasone was lower in the netupitant arms of the study to achieve exposure similar to that in the

palonosetron group (because netupitant is a moderate CYP3A4 inhibitor, and dexamethasone is a major CYP3A4 substrate). Patients taking netupitant received oral dexamethasone 12 mg given 30 minutes before chemotherapy (cisplatin) on Day 1, followed by 4 mg twice daily (BID) on Days 2 to 4, whereas patients taking palonosetron alone received dexamethasone 20 mg on Day 1 followed by 8 mg BID on Days 2 to 4. Patients in the exploratory arm received dexamethasone at the same doses as the netupitant arms. Rescue treatment for nausea and vomiting post-HEC was permitted but was considered a treatment failure. Each patient completed a diary from the time of cisplatin infusion through the morning of Day 6 detailing emetic episodes, severity of nausea, concomitant medications, and overall satisfaction. Please see **Table III-1** for the efficacy endpoints and safety assessments evaluated.

Inclusion and Exclusion Criteria: The major inclusion and exclusion criteria are summarized in **Table III-2**.

Table III-2. Study Inclusion and Exclusion Criteria

Inclusion Criteria	• ≥ 18 years of age • Histologically or cytologically confirmed malignant disease featuring solid tumor(s) • Chemotherapy naïve, Karnofsky index ≥ 70% • Scheduled to receive HEC on Day 1 with a single dose of cisplatin ≥ 50 mg/m^2 either alone or in combination with other chemotherapy agents
Exclusion Criteria	• Scheduled to receive one of the following: – MEC or HEC on Days 2 to 5 – Moderately or highly emetogenic radiotherapy within 1 week of Day 1 or on Days 2 to 5 – Bone marrow or stem cell transplant • Antiemetic drug use within 24 hours of treatment or systemic corticosteroids within 72 hours of Day 1 treatment • Vomiting, retching, or more than mild nausea within 24 hours before Day 1 • History of serious cardiovascular disease or predisposition to cardiac conduction abnormalities, with the exception of incomplete right bundle branch block • Chronic use of CYP3A4 substrates, inhibitors, or inducers, or intake of substrates or inhibitors within 1 week of Day 1, or intake of inducers within 4 weeks of Day 1

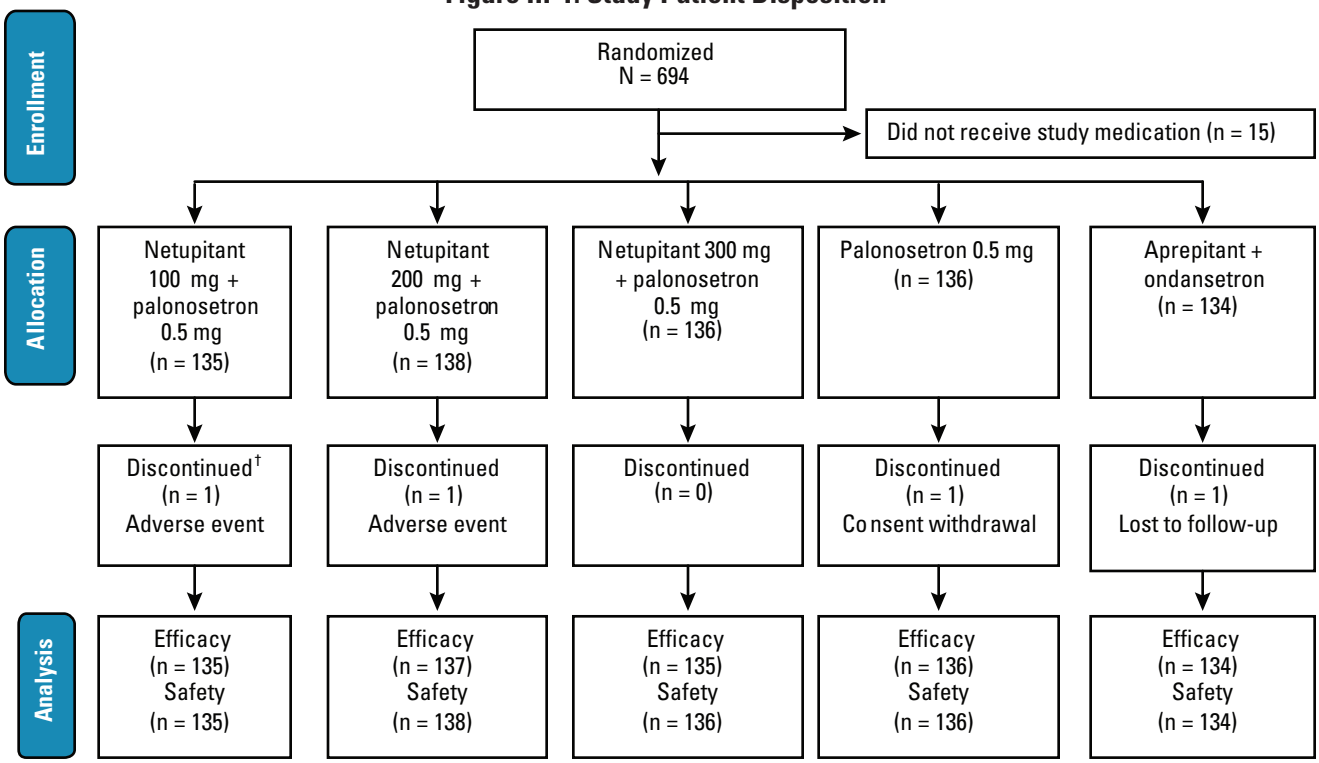
CYP = cytochrome P450; HEC = highly emetogenic chemotherapy; MEC = moderately emetogenic chemotherapy

Results

Patient Disposition and Demographics: Patient disposition is shown in **Figure III-1**. A total of 694 patients were randomized, but 15 did not receive a dose of the study drugs. Two patients were excluded from the efficacy analysis (one discontinued because of an AE; the reason for the other discontinuation was not specified); 677 were included in the intent-to-treat (ITT) efficacy analysis. The safety evaluation included 679 patients.

Patient baseline characteristics were comparable between the five treatment groups. Lung/respiratory cancer and head and neck cancer were the most commonly reported malignant diseases. All five treatment groups were similar with regard to type and dose of chemotherapy administered, with a median cisplatin dose of 75 mg/m^2 in each group.

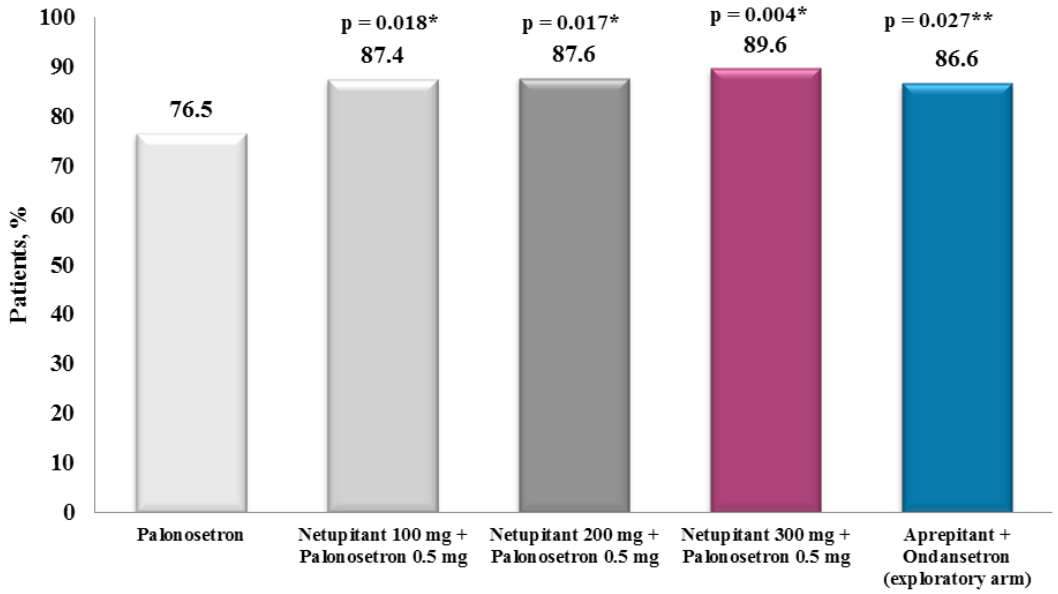
Figure III-1. Study Patient Disposition



†Death not related to study medication

Primary Efficacy Endpoint: CR rates (defined as no emesis and no rescue medication use) in the netupitant treatment arms were significantly greater than with palonosetron alone during the overall phase after HEC (**Figure III-2**).

Figure III-2. Complete Response Rates, Overall Phase[53]



Based on full analysis set of 677 patients.
*p value from logistic regression analysis vs palonosetron.
**p value from post hoc logistic regression analysis vs palonosetron.

Secondary Efficacy Endpoints: During the acute phase, more patients receiving netupitant 300 mg vs palonosetron alone experienced a CR (98.5% vs 89.7%; $p \leq 0.01$). In the delayed phase, more patients receiving netupitant 100 mg, netupitant 200 mg, and netupitant 300 mg vs palonosetron alone experienced a CR ($p \leq 0.05$, $p \leq 0.01$, and $p \leq 0.05$, respectively) (**Table III-3**).

Table III-3. Secondary Efficacy Endpoints

	Palonosetron (n = 136)	Netupitant 100 mg + Palonosetron 0.5 mg (n = 135)	Netupitant 200 mg + Palonosetron 0.5 mg (n = 136)	Netupitant 300 mg + Palonosetron 0.5 mg (n = 135)	Aprepitant + Ondansetron (exploratory arm) (n = 134)
Complete response					
Acute	89.7%	93.3%	92.7%	98.5%†	94.8%
Delayed	80.1%	90.4%*	91.2%†	90.4%*	88.8%*
No emesis					
Acute	89.7%	93.3%	92.7%	98.5%†	94.8%
Delayed	80.1%	90.4%*	91.2%†	91.9%†	89.6%*
Overall	76.5%	87.4%*	87.6%*	91.1%†	87.3%
No significant nausea					
Acute	93.4%	94.1%	94.2%	98.5%*	94.0%
Delayed	80.9%	81.5%	89.8%*	90.4%†	88.1%
Overall	79.4%	80.0%	86.1%	89.6%*	85.8%
Complete protection					
Acute	87.5%	89.6%	88.3%	97.0%†	89.6%
Delayed	73.5%	80.0%	87.6%†	84.4%*	82.1%
Overall	69.9%	76.3%	80.3%*	83.0%†	78.4%

*$p \leq 0.05$ from logistic regression analysis vs palonosetron; not adjusted for multiple comparisons, with exception of primary endpoint (CR overall).
†$p \leq 0.01$ from logistic regression analysis vs palonosetron; not adjusted for multiple comparisons, with exception of primary endpoint (CR overall).
‡$p \leq 0.05$ from post hoc logistic regression analysis vs palonosetron.

Study Limitations: None reported.

Safety: At least one AE was reported by 40.7% of patients receiving netupitant 100 mg, 51.4% of patients receiving netupitant 200 mg, 50.0% of patients receiving netupitant 300 mg, and 49.3% of patients receiving palonosetron alone, with the majority of AEs being mild/moderate in intensity. The most common treatment-emergent, drug-related AEs reported in all treatment groups are shown in **Table III-4.**

Five patients experienced serious AEs (one receiving netupitant 100 mg, one receiving netupitant 200 mg, three receiving palonosetron alone). Of those, only one (in the patient receiving netupitant 200 mg) was assessed to be related to the study medication. That patient lost consciousness, recovered within 30 minutes, and discontinued study treatment. There was one death due to multiple organ failure. The treatment groups had comparable rates of patients who developed treatment-emergent ECG abnormalities.

Table III-4. Most Common Treatment-Related Adverse Events (≥ 2% Incidence in any Group)

Adverse Event	Netupitant 100 mg + Palonosetron (n = 135)	Netupitant 200 mg + Palonosetron (n = 138)	Netupitant 300 mg + Palonosetron (n = 136)	Palonosetron (n = 136)	Aprepitant + Ondansetron (exploratory arm) (n = 134)
Hiccups	3.7%	3.6%	5.1%	3.7%	0%
Headache	0.7%	2.2%	0.7%	1.5%	2.2%
Leukocytosis	1.5%	0.7%	1.5%	2.2%	0.7%
ALT increased	0.7%	2.2%	1.5%	0.7%	1.5%
AST increased	0.7%	2.2%	0.7%	0.7%	1.5%
Dyspepsia	0%	2.9%	0.7%	1.5%	0%
Bradycardia	0.7%	0%	0%	0%	2.2%
Bundle branch block	0.7%	0%	2.2%	0%	0%
Anorexia	0%	0%	0.7%	2.2%	0%

ALT = alanine aminotransferase; AST = aspartate aminotransferase

AKYNZEO for the Prevention of CINV After A/C Chemotherapy
Study NEPA 08-18
Aapro et al, 2014[15]

Key Findings

This was a Phase III, randomized, double-blind, multicenter study comparing the efficacy and tolerability of single oral doses of AKYNZEO vs oral palonosetron 0.5 mg in preventing CINV after A/C (N = 1455).

Primary Endpoint

More patients receiving AKYNZEO vs palonosetron had a CR during the delayed phase (AKYNZEO, 76.9%; palonosetron, 69.5%; p = 0.001) (**Figure III-4**).

Secondary Endpoints

- During the acute phase and the overall phase, more patients receiving AKYNZEO vs palonosetron experienced a CR (acute, 88.4% vs 85% [p = 0.047]; overall, 74.3% vs 66.6% [p = 0.001]).
- Significantly more patients in the AKYNZEO group reported no emesis during the acute, delayed, and overall phases compared with the palonosetron group (p = 0.025, p = 0.004, and p < 0.001, respectively).
- Significantly more patients in the AKNZEO group reported no significant nausea during the delayed and overall phases, but not the acute phase, compared with the palonosetron group(delayed, p = 0.014; overall, p = 0.020).
- CP was achieved by more patients who received AKYNZEO vs palonosetron during the delayed and overall phases (p = 0.005, and p = 0.020, respectively).
- FLIE questionnaire results showed that a greater proportion of patients receiving AKYNZEO vs patients receiving palonosetron reported no impact on daily living from CINV (nausea domain, p = 0.015; vomiting domain, p =0.001; combined domain, p = 0.005).

Safety

- The most common treatment-emergent, drug-related AEs reported in the treatment groups were headache (AKYNZEO, 3.3%; palonosetron, 3.0%) and constipation (AKYNZEO, 2.1%; palonosetron, 2.1%).
- The treatment groups had comparable rates of patients who developed treatment-emergent ECG abnormalities.

Objective: To compare the efficacy and tolerability of single oral doses of AKYNZEO (netupitant 300 mg combined with oral palonosetron 0.5 mg) vs oral palonosetron 0.5 mg alone in preventing CINV after A/C in patients naïve to chemotherapy.

Patients and Methods: This was a Phase III, randomized, double-blind, double-dummy, multicenter, parallel-group study conducted at 177 sites in 15 countries. Patients were randomized in a 1:1 ratio to receive a single oral dose of one of the following:

- AKYNZEO (netupitant 300 mg plus palonosetron 0.5 mg)
- Oral palonosetron 0.5 mg

Corticosteroid treatment with dexamethasone was included in both groups; the dose of dexamethasone was lower in the AKYNZEO arm of the study to achieve exposure similar to that in the palonosetron group (because netupitant is a moderate CYP3A4 inhibitor, and dexamethasone is a major CYP3A4 substrate). Patients taking AKYNZEO received oral dexamethasone 12 mg given 30 minutes before chemotherapy on Day 1, whereas patients taking palonosetron alone received dexamethasone 20 mg on Day 1. Rescue treatment for nausea and vomiting postchemotherapy was permitted but was considered a treatment failure. Each patient completed a diary from the time of chemotherapy infusion through the morning of Day 6 detailing emetic episodes, severity of nausea, and use of rescue medications. On Day 6, each patient completed the FLIE questionnaire to assess the impact of CINV on daily life. Please see **Table III-1** for the efficacy endpoints and safety assessments evaluated. After completing Cycle 1, patients could choose to participate in a multiple-cycle extension study during which they would receive the same assigned treatment.

Inclusion and Exclusion Criteria: The major inclusion and exclusion criteria are summarized in **Table III-5**.

Table III-5. Study Inclusion and Exclusion Criteria

Inclusion Criteria	• ≥ 18 years of age • Chemotherapy naïve • ECOG performance status of 0, 1, or 2 • Scheduled to receive an A/C regimen on Day 1 for treatment of a solid malignant tumor
Exclusion Criteria	• Scheduled to receive one of the following: – HEC from Days 1 to 5 or additional MEC on Days 2 to 5 – Radiotherapy to the abdomen or pelvis within 1 week of Day 1 or on Days 1 to 5 – Bone marrow or stem cell transplant • Antiemetic drug use within 24 hours of treatment • Vomiting, retching, or more than mild nausea within 24 hours before Day 1 • History of serious cardiovascular disease or predisposition to cardiac conduction abnormalities, with the exception of incomplete right bundle branch block • Scheduled to receive CYP3A4 inhibitors, inducers, or certain substrates during the study, or intake of strong or moderate inhibitors within 1 week of Day 1, or intake of inducers within 4 weeks of Day 1

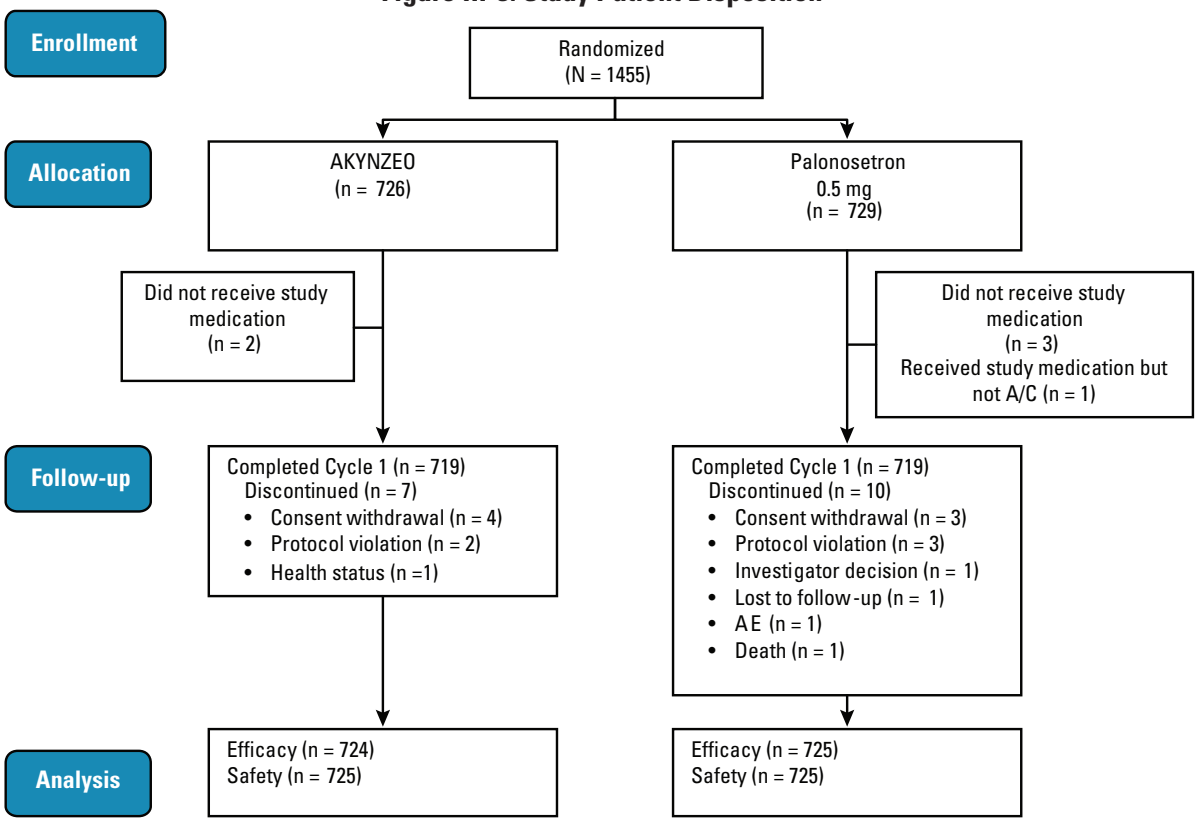
A/C = anthracycline/cyclophosphamide; CYP = cytochrome P450; ECOG = Eastern Cooperative Oncology Group; HEC = highly emetogenic chemotherapy; MEC = moderately emetogenic chemotherapy

Results

Patient Disposition and Demographics: Patient disposition is shown in **Figure III-3**. A total of 1455 patients were randomized, but 5 did not receive a dose of the study drugs and 1 patient received the study drugs but not A/C; 1449 patients were included in the ITT efficacy analysis. The safety evaluation included 1450 patients.

Patient baseline characteristics were comparable between the treatment groups. Breast cancer was the most commonly reported malignant disease. The treatment groups were similar with regard to type of chemotherapy administered and Eastern Cooperative Oncology Group performance status (ECOG PS).

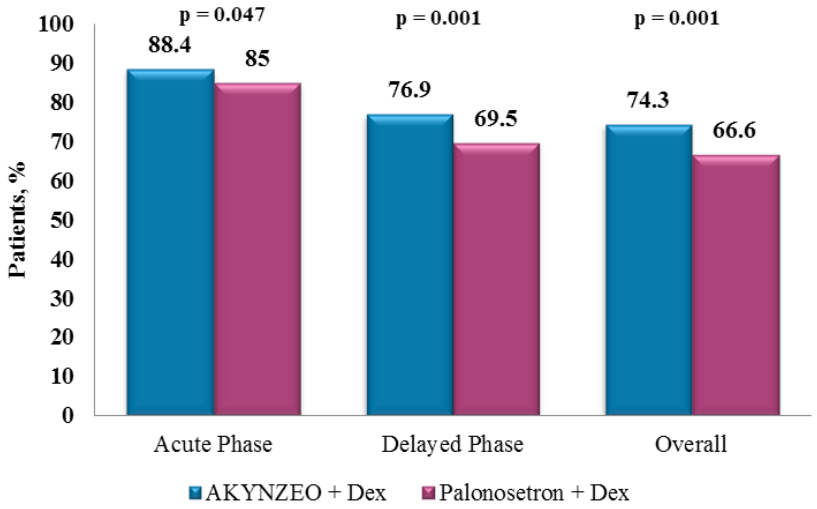
Figure III-3. Study Patient Disposition



A/C = anthracycline/cyclophosphamide

Primary Efficacy Endpoint: During the delayed phase, more patients receiving AKYNZEO vs palonosetron had a CR (defined as no emesis and no rescue medication use) (AKYNZEO, 76.9%; palonosetron, 69.5%; p = 0.001) (**Figure III-4**).

Figure III-4. Complete Response Rates*[54]



Based on full analysis set of 1449 patients.
*CR = no emesis, no rescue medication
Dex = dexamethasone

Secondary Efficacy Endpoints: During the acute phase and the overall phase, more patients receiving AKYNZEO vs palonosetron experienced a CR (acute, p = 0.047; overall, p = 0.001) (**Figure III-4**). Rates of no emesis, no significant nausea, and CP were significantly greater for AKYNZEO than for palonosetron during the delayed and overall phases (**Table III-6**). Rates of no emesis in the acute phase were also significantly greater in the AKYNZEO group vs the palonosetron group.

Table III-6. Secondary Efficacy Endpoints[15]

	AKYNZEO (n = 724)	Palonosetron (n = 725)	p Value
No emesis			
Acute phase	90.9%	87.3%	0.025
Delayed phase	81.8%	75.6%	0.004
Overall phase	79.8%	72.1%	< 0.001
No significant nausea			
Acute phase	87.3%	87.9%	0.747
Delayed phase	76.9%	71.3%	0.014
Overall phase	74.6%	69.1%	0.020
Complete protection			
Acute phase	82.3%	81.1%	0.528
Delayed phase	67.3%	60.3%	0.005
Overall phase	63.8%	57.9%	0.020

FLIE questionnaire results showed that a greater proportion of patients receiving AKYNZEO vs patients receiving palonosetron reported no impact on daily living from CINV (nausea domain, p = 0.015; vomiting domain, p = 0.001; combined domain, p = 0.005).

Study Limitations: None reported.

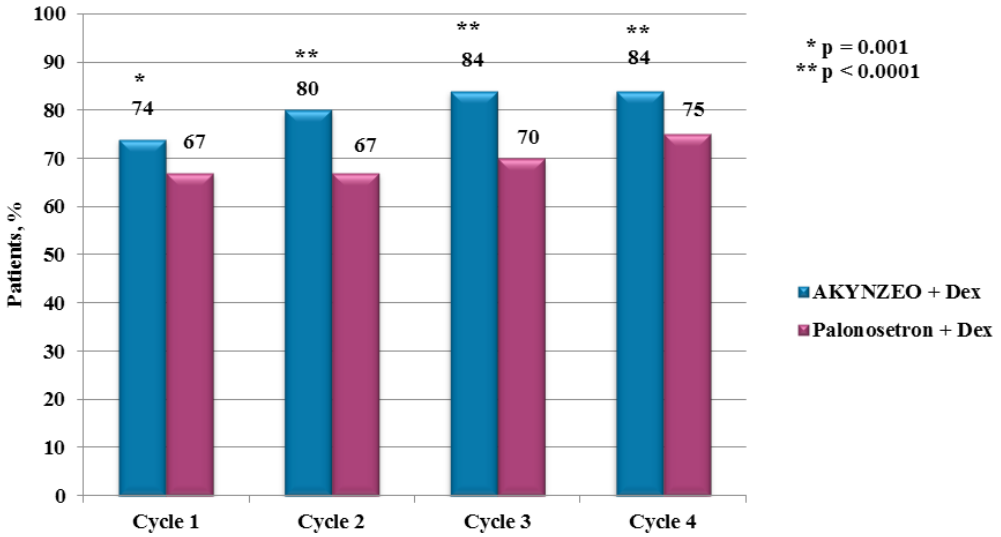
Safety: At least one AE was reported by 76.0% of patients receiving AKYNZEO and 69.9% of patients receiving palonosetron, with the majority of AEs being mild/moderate in intensity. The most common treatment-emergent, drug-related AEs reported in the treatment groups were headache (AKYNZEO, 3.3%; palonosetron, 3.0%) and constipation (AKYNZEO, 2.1%; palonosetron, 2.1%). No treatment-related AEs led to discontinuation in the AKYNZEO group vs two discontinuations in the palonosetron group.

Serious AEs were reported by 25 patients (13 AKYNZEO, 12 palonosetron), and none were assessed to be related to the study medication. There were no deaths in the AKYNZEO group reported during the study. The treatment groups had comparable rates of patients who developed treatment-emergent ECG abnormalities.

Prevention of CINV During Repeated A/C Cycles Aapro et al, 2014[52]

Following completion of Cycle 1, patients had the option to enter a multiple-cycle extension phase. Patients received the same treatment as assigned in Cycle 1. A total of 1286 patients participated in the extension phase: 635 treated with AKYNZEO and 651 treated with palonosetron. A total of 5969 total chemotherapy cycles were completed; 76% of patients completed at least 4 cycles. Across all cycles, overall CR rates were significantly greater in the AKYNZEO group compared to the palonosetron group (**Figure III-5**).

Figure III-5. Overall Complete Response[52]



	Cycle 1	Cycle 2	Cycle 3	Cycle 4
AKYNZEO + Dex, n	724	635	598	551
Palonosetron + Dex, n	725	651	606	560

Dex = dexamethasone

Overall, rates of no emesis and no significant nausea were significantly greater in the AKYNZEO group compared to the palonosetron group across all cycles (**Table III-7**).

Table III-7. Rates of No Emesis and No Significant Nausea (Overall Phase)[52]

	No Emesis			No Significant Nausea*		
	AKYNZEO + Dex	Palonosetron + Dex	p Value	AKYNZEO + Dex	Palonosetron + Dex	p Value
Cycle 1	80%	72%	< 0.001	75%	69%	0.020
Cycle 2	86%	74%	< 0.0001	77%	72%	0.018
Cycle 3	88%	77%	< 0.0001	78%	73%	0.034
Cycle 4	87%	79%	0.0003	80%	75%	0.042

Based on full analysis set of 1449; analyses not adjusted for multiplicity
*Maximum of < 25 mm of 100 mm VAS
Dex = dexamethasone; VAS = visual analog scale

Adverse event rates across multiple cycles were similar between the 2 treatment groups (**Table III-8**).

Table III-8. Adverse Event Rates Across Cycles[52]

Patients with AEs, %	Treatment-Emergent AEs		Treatment-Related AEs	
Cycle (n = AKYNZEO/Palonosetron)	AKYNZEO + Dex	Palonosetron + Dex	AKYNZEO + Dex	Palonosetron + Dex
Cycle 1 (n = 725/725)	76.0%	69.9%	8.1%	7.2%
Cycle 2 (n = 635/651)	65.0%	61.4%	6.5%	4.5%
Cycle 3 (n = 598/605)	57.4%	53.2%	3.5%	3.5%
Cycle 4 (n = 550/561)	46.4%	39.0%	4.0%	1.2%
Cycle 5 (n = 271/249)	40.6%	39.8%	2.6%	0.8%
Cycle 6 (n = 197/191)	31.0%	30.9%	1.5%	0.5%

AE = adverse event; Dex = dexamethasone

AKYNZEO for the Prevention of CINV Over Repeated Cycles of Chemotherapy
Study NEPA 10-29
Gralla et al, 2014[18]

Key Findings

This was a Phase III, randomized, double-blind, multicenter study comparing the safety of single oral doses of AKYNZEO vs oral palonosetron/aprepitant in preventing CINV after multiple cycles of MEC or HEC (N = 413).

Safety

- The most common treatment-emergent, drug-related AEs reported in the treatment groups were constipation (AKYNZEO, 3.6%; palonosetron/aprepitant, 1.0%) and headache (AKYNZEO, 1.0%; palonosetron/aprepitant, 1.0%).
- Adverse event rates did not increase over multiple cycles, and the incidence, type, and frequency of treatment-emergent AEs was similar for both groups throughout the study.
- The treatment groups had comparable rates of patients who developed treatment-emergent ECG abnormalities.

Efficacy Endpoints

CR rates during the overall phase were high in both treatment groups during all cycles of chemotherapy, ranging from 81% to 92% in the AKYNZEO group and from 76% to 88% in the palonosetron/aprepitant group (**Figure III-7**). Although no formal statistical comparisons were performed, CR rates were numerically greater for patients receiving AKYNZEO during the overall phase and the delayed phase. CR rates were similar for the treatment groups during the acute phase.Among patients in the AKYNZEO group, CR rates during the overall period were similar for patients receiving HEC or MEC across all treatment cycles.

Objective: To assess the safety and describe the efficacy of AKYNZEO (netupitant 300 mg/oral palonosetron 0.5 mg) over multiple cycles of MEC or HEC in patients naïve to chemotherapy.

Patients and Methods: This was a Phase III, randomized, double-blind, double-dummy, multicenter, parallel-group study conducted at 59 sites in 10 countries. The palonosetron plus aprepitant arm was included as a control to help interpret any unexpected safety findings in the AKYNZEO arm. Patients were randomized in a 3:1 ratio to receive oral doses of one of the following:

- AKYNZEO on Day 1
- Oral palonosetron 0.5 mg on Day 1 plus aprepitant (125 mg Day 1, 80 mg Days 2 to 3)

Corticosteroid treatment with dexamethasone was included in both groups at the same doses, based on the emetogenic potential of the chemotherapy regimen. Patients undergoing MEC received dexamethasone 12 mg 30 minutes before chemotherapy on Day 1, and patients undergoing HEC received dexamethasone 12 mg on Day 1 plus 8 mg on Days 2 to 4. Rescue treatment for nausea and vomiting postchemotherapy was permitted but was considered a treatment failure. Each patient completed a diary from the time of chemotherapy infusion through the morning of Day 6 detailing emetic episodes, severity of nausea, and use of rescue medications. Please see **Table III-1** for the safety assessments and efficacy endpoints evaluated. There was no prespecified limit to the number of consecutive chemotherapy cycles allowed.

Inclusion and Exclusion Criteria: The major inclusion and exclusion criteria are summarized in **Table III-9**.

Table III-9. Study Inclusion and Exclusion Criteria

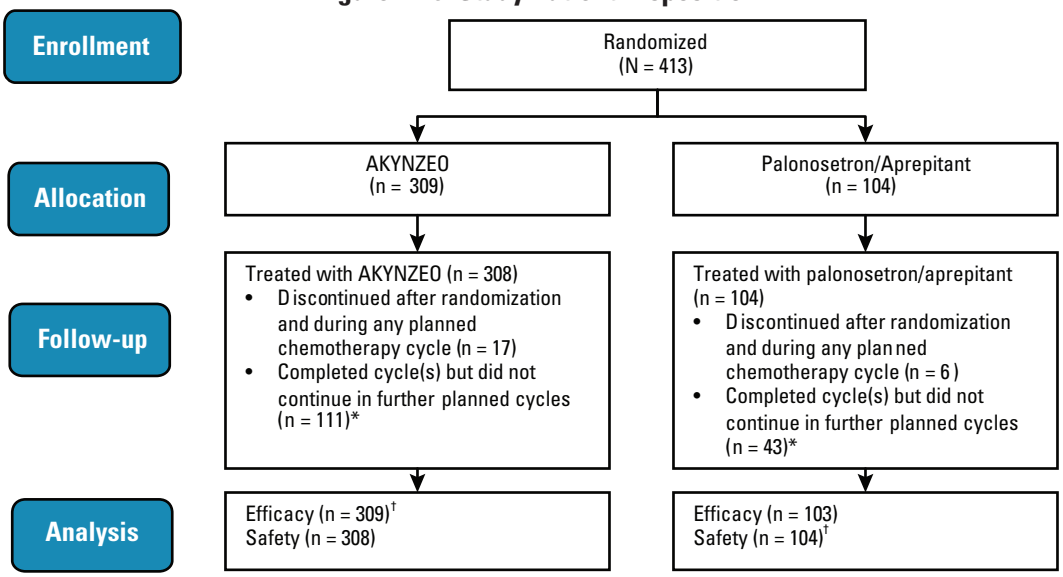
Inclusion Criteria	• ≥ 18 years of age • Chemotherapy naïve • ECOG PS 0 to 2 • Scheduled to receive repeated consecutive courses of chemotherapy with either HEC (cisplatin, mechlorethamine, streptozocin, cyclophosphamide ≥ 1500 mg/m^2, carmustine, dacarbazine) or MEC (oxaliplatin, carboplatin, epirubicin, idarubicin, ifosfamide, irinotecan, daunorubicin, doxorubicin, cyclophosphamide [< 1500 mg/m^2], cytarabine [> 1 g/m^2], azacitidine, alemtuzumab, bendamustine, or clofarabine) for treatment of a malignant tumor
Exclusion Criteria	• Diagnosis of breast cancer and scheduled to receive A/C • Scheduled to receive HEC or MEC on Days 2 to 5, bone marrow or stem cell transplant • History or predisposition to cardiac conduction abnormalities, torsades de pointes or severe cardiovascular disease • Scheduled to receive CYP3A4 inhibitors, inducers, or certain substrates during the study, or intake of strong or moderate inhibitors within 1 week of Day 1, or intake of inducers within 4 weeks of Day 1 • Previously received an NK_1 receptor antagonist • Known hypersensitivity or contraindication to 5-HT_3 receptor antagonist or dexamethasone

5-HT_3 = serotonin receptor subtype 3; A/C = anthracycline/cyclophosphamide; CYP = cytochrome P450, ECOG PS = Eastern Cooperative Oncology Group performance status; HEC = highly emetogenic chemotherapy; MEC = moderately emetogenic chemotherapy; NK_1 = neurokinin-1 receptor

Results

Patient Disposition and Demographics: Patient disposition is shown in **Figure III-6**. Patient baseline characteristics were consistent between the treatment groups across cycles. The AKYNZEO group found poorer cancer prognostic variables, with greater proportions of patients with lung/respiratory tract cancers (40% vs 31%) and metastatic cancer (52% vs 43%), and with concomitant disease (78% vs 62%) compared to patients in the palonosetron/aprepitant group. In both groups, approximately 76% of patients received MEC, and 24% of patients received HEC. The treatment groups were similar with regard to ECOG PS.

Figure III-6. Study Patient Disposition



*The vast majority discontinued due to the study closure which occurred when the last patient enrolled had completed his/her final chemotherapy cycle; these patients were allowed to complete their current cycle but not enter any further cycles.
†One patient who was randomized to AKYNZEO received palonosetron/aprepitant throughout the study. Following the ITT principle, this patient was analyzed in the AKYNZEO group for the full analysis set (FAS; n = 309) and the palonosetron/aprepitant group for the safety population (n = 104).

Safety: During Cycle 1, at least one AE was reported by 64.6% of patients receiving AKYNZEO and 61.5% of patients receiving palonosetron/aprepitant. During the entire multiple-cycle study period, 86.0% of patients receiving AKYNZEO and 91.3% of patients receiving palonosetron/aprepitant reported AEs. The majority of AEs were mild/moderate in intensity. The most common treatment-emergent, drug-related AEs were constipation (AKYNZEO, 3.6%; palonosetron/aprepitant, 1.0%) and headache (AKYNZEO, 1.0%; palonosetron/aprepitant, 1.0%). AE rates did not increase over multiple cycles (Table III-10). The incidence, type, and frequency of treatment-emergent AEs were similar for both groups throughout the study.

Table III-10. Treatment-Related Adverse Events Across Cycles[18]

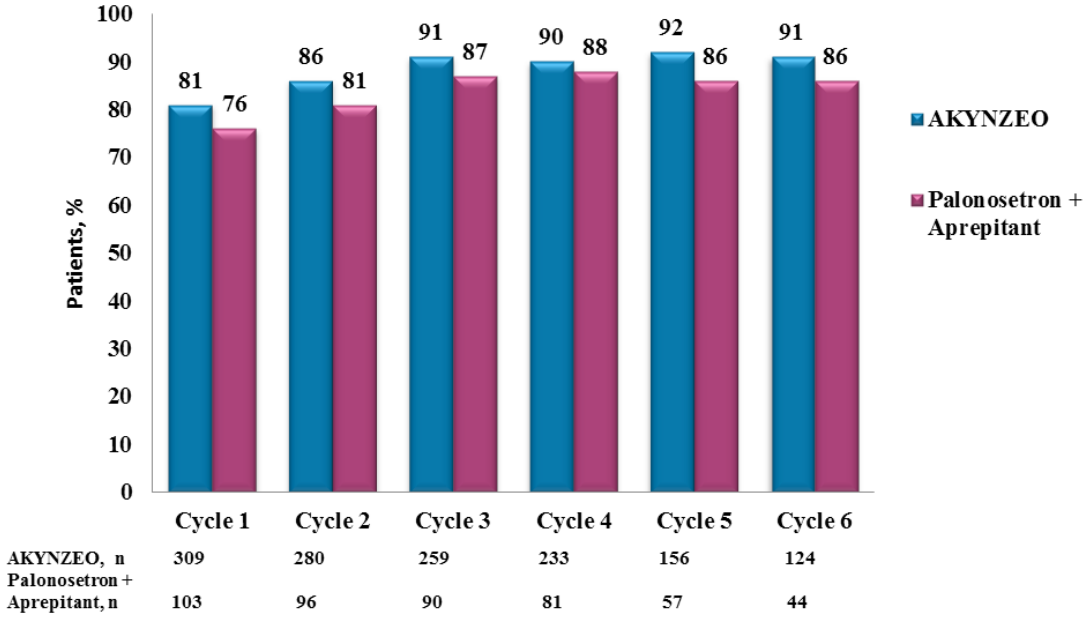
Patients With AEs, %	Treatment-Emergent AEs		Treatment-Related AEs	
Cycle (n = AKYNZEO/Aprepitant)	AKYNZEO	Palonosetron + Aprepitant	AKYNZEO	Palonosetron + Aprepitant
Cycle 1 (n = 308/104)	64.6%	61.5%	5.2%	2.9%
Cycle 2 (n = 279/96)	54.8%	57.3%	4.3%	1.0%
Cycle 3 (n = 258/91)	50.4%	58.2%	1.9%	2.2%
Cycle 4 (n = 232/81)	43.5%	48.1%	1.3%	1.2%
Cycle 5 (n = 156/57)	45.5%	57.9%	0.6%	1.8%
Cycle 6 (n = 124/43)	34.7%	32.6%	1.6%	0.0%

Cardiac Safety:

Changes from baseline in 12-lead ECGs at 5 and 24 hours postdose were similar between the groups across all cycles. In both groups, any corrected QT (QTc) interval prolongations were transient, returning to baseline values by the examination at 120 hours. Fridericia QTc (QTcF) increases > 60 milliseconds (ms) were rare (one AKYNZEO-treated patient in Cycles 1, 3, 4, and 5; one palonosetron/aprepitant-treated patient in Cycles 1 and 4). QTcF increases > 500 ms occurred in one AKYNZEO-treated patient in Cycles 1, 3, and 4, and in one palonosetron/aprepitant-treated patient in Cycle 6.

Efficacy Endpoints: CR rates (defined as no emesis and no rescue medication use) during the overall phase were high in both treatment groups during all 6 cycles of chemotherapy (**Figure III-7**). No formal statistical comparisons were performed. CR rates were numerically greater for patients receiving AKYNZEO during the overall phase and the delayed phase. CR rates were similar for the treatment groups, during the acute phase.

Figure III-7. Complete Response Rates, Overall Phase[55]



No significant nausea (< 25 mm on a 100-mm VAS scale) was reported by high numbers of patients in both groups during the overall phase (AKYNZEO, range 84% to 92% across cycles; palonosetron/aprepitant, 81% to 87%). A similar numerical advantage was found in the delayed phase.

Study Limitations: Not reported.

Table III-11. Supporting Clinical Evidence Table

Study	Design	Inclusion/Exclusion Criteria	Treatment	Endpoints	Results/Comments
PIVOTAL TRIALS					
AKYNZEO for the Prevention of CINV After HEC ***Study NEPA 07-07*** ***Hesketh et al, 2014***[51]	R, DB, DD, PG, MC, MN Phase II study N = 694 chemotherapy-naïve patients scheduled to receive cisplatin-based HEC FAS (n = 677) Safety analysis (n = 679) 1 cycle After completeing cycle 1, patients could choose to participate in a multiple-cycle extension study	Inclusion: Age ≥ 18 years, histologically or cytologically confirmed malignant disease featuring solid tumor(s); chemotherapy naïve; scheduled to receive HEC (including cisplatin ≥ 50 mg/m^2); KPS ≥ 70% Exclusion: Scheduled to receive MEC or HEC on Days 2 to 5, or moderately or highly emetogenic radiotherapy on Days 2 to 5 or within 1 week of Day 1, or bone marrow or stem cell transplant; antiemetic use within 24 hours of treatment or systemic corticosteroids within 72 hours of treatment; vomiting, retching, or more than mild nausea 24 hours before chemotherapy; history of serious CV disease or predisposition to cardiac conduction abnormalities with the exception of incomplete right bundle branch block; chronic use of CYP3A4 substrates, inhibitors, inducers or intake of substrates, inhibitors within 1 week of treatment or inducers within 4 weeks of treatment		Primary: CR overall phase Secondary: CR during the acute and delayed phases; CP during the acute, delayed, and overall phases; no emesis, no significant nausea Safety assessments: AEs; vital sign measurements; laboratory tests; physical examination; ECG recordings	***Primary endpoint:*** **CR in the Overall Phase** **Treatment Group** / **CR (p value vs palonosetron)** Palonosetron: 76.5% Netupitant 100 mg/palonosetron: 87.4% (p = 0.018) Netupitant 200 mg/palonosetron: 87.6% (p = 0.017) Netupitant 300 mg/palonosetron: 89.6% (p = 0.004) Aprepitant + ondansetron (exploratory arm): 86.6% (p = 0.027) ***Key Secondary endpoints:*** **Treatment Group** / **CR (p value vs palonosetron)** **Acute Phase** / **Delayed Phase** Palonosetron: 89.7% / 80.1% Netupitant 100 mg/palonosetron: 93.3% / 90.4% (p ≤ 0.05) Netupitant 200 mg/palonosetron: 92.7% / 91.2% (p ≤ 0.01) Netupitant 300 mg/palonosetron: 98.5% (p ≤ 0.01) / 90.4% (p ≤ 0.05 Aprepitant + ondansetron (exploratory arm: 94.8% / 88.8% (p ≤ 0.05) **No Emesis** Acute: 89.7%; 93.3%; 92.7%; 98.5%†; 94.8% Delayed: 80.1%; 90.4%*; 91.2%†; 91.9%†; 89.6%* Overall: 76.5%; 87.4%*; 87.6%*; 91.1%†; 87.3% **No Significant Nausea** Acute: 93.4%; 94.1%; 94.2%; 98.5%*; 94.0% Delayed: 80.9%; 81.5%; 89.8%*; 90.4%†; 88.1% Overall: 79.4%; 80.0%; 86.1%; 89.6%*; 85.8% **Complete Protection** Acute: 87.5%; 89.6%; 88.3%; 97.0%†; 89.6% Delayed: 73.5%; 80.0%; 87.6%†; 84.4%*; 82.1% Overall: 69.9%; 76.3%; 80.3%*; 83.0%†; 78.4% Palonosetron / Netupitant 100 mg + Palonosetron / Netupitant 200 mg + Palonosetron / Netupitant 300 mg + Palonosetron / Aprepitant + Ondansetron (exploratory arm) *p ≤ 0.05 from logistic regression analysis vs palonosetron; not adjusted for multiple comparisons, with exception of primary endpoint (CR overall); †p ≤ 0.01 from logistic regression analysis vs palonosetron; not adjusted for multiple comparisons, with exception of primary endpoint (CR overall); ‡ p ≤ 0.05 from post hoc logistic regression analysis vs palonosetron

Study	Design	Inclusion/Exclusion Criteria	Treatment	Endpoints	Results/Comments
					Safety: • The most common treatment-emergent, drug-related AEs reported in all treatment groups were hiccups (netupitant 100 mg, 3.7%; netupitant 200 mg, 3.6%; netupitant 300 mg, 5.1%; palonosetron alone, 3.7%) and headache (netupitant 100 mg, 0.7%; netupitant 200 mg, 2.2%; netupitant 300 mg, 0.7%; palonosetron alone, 1.5%). • The treatment groups had comparable rates of patients who developed treatment-emergent ECG abnormalities.
AKYNZEO for the Prevention of CINV After A/C ***Study NEPA 08-18*** ***Aapro et al, 2014[15]***	R, DB, DD, PG, MC, MN Phase III study N = 1455 adult patients with cancer scheduled to receive A/C ITT efficacy analysis (n = 1449) Safety analysis (n = 1450) 1 cycle	Inclusion: Age ≥ 18 years; chemotherapy naïve; scheduled to receive A/C for treatment of solid malignant tumor; ECOG PS 0 to 2 Exclusion: Scheduled to receive HEC on Days 1 to 5 or additional MEC on Days 2 to 5, or radiotherapy to abdomen or pelvis within 1 week of Day 1 or on Days 1 to 5, or bone marrow or stem cell transplant; antiemetic drug use within 24 hours of treatment; vomiting, retching, or more than mild nausea 24 hours before chemotherapy; history of serious CV disease or predisposition to cardiac conduction abnormalities with the exception of incomplete right bundle branch block; scheduled use of CYP3A4 substrates, inhibitors, inducers during the study or intake of strong/moderate inhibitors within 1 week of treatment or inducers within 4 weeks of treatment		Primary: CR (no emetic episode and no rescue medication) in preventing nausea and vomiting during the delayed phase Secondary: CR during acute phase, CR overall, CP (no emetic episode, no need for rescue medication, and no significant nausea) during the acute, delayed, and overall phases; no emesis, no significant nausea; FLIE Safety assessments: AEs; vital sign measurements; laboratory tests; physical examination; ECG recordings	***Primary endpoint:*** **CR in the Delayed Phase** **AKYNZEO**: 76.9%; **Palonosetron**: 69.5%; **p Value**: 0.001 ***Secondary endpoints:*** **CR, acute phase**: AKYNZEO 88.4%, Palonosetron 85.0%, p Value 0.047 **CR, overall**: AKYNZEO 74.3%, Palonosetron 66.6%, p Value 0.001 **No emesis** Acute phase: AKYNZEO 90.9%, Palonosetron 87.3%, p Value 0.025 Delayed phase: AKYNZEO 81.8%, Palonosetron 75.6%, p Value 0.004 Overall phase: AKYNZEO 79.8%, Palonosetron 72.1%, p Value < 0.001 **No significant nausea** Acute phase: AKYNZEO 87.3%, Palonosetron 87.9%, p Value 0.747 Delayed phase: AKYNZEO 76.9%, Palonosetron 71.3%, p Value 0.014 Overall phase: AKYNZEO 74.6%, Palonosetron 69.1%, p Value 0.020 **Complete protection** Acute phase: AKYNZEO 82.3%, Palonosetron 81.1%, p Value 0.528 Delayed phase: AKYNZEO 67.3%, Palonosetron 60.3%, p Value 0.005 Overall phase: AKYNZEO 63.8%, Palonosetron 57.9%, p Value 0.020 • FLIE questionnaire results showed that a greater proportion of patients receiving AKYNZEO vs palonosetron reported no impact on daily living from CINV (nausea domain, p = 0.015; vomiting domain, p = 0.001; combined domain, p = 0.005). ***Safety:*** • The most common treatment-emergent, drug-related AEs reported in the treatment groups were headache (AKYNZEO, 3.3%; palonosetron, 3.0%) and constipation (AKYNZEO, 2.1%; palonosetron, 2.1%). • The treatment groups had comparable rates of patients who developed treatment-emergent ECG abnormalities.

<table>
<tr><th>Study</th><th>Design</th><th>Inclusion/Exclusion Criteria</th><th>Treatment</th><th>Endpoints</th><th>Results/Comments</th></tr>
<tr>
<td>AKYNZEO for the Prevention of CINV During Repeated A/C Cycles

Aapro et al, 2014[52]</td>
<td>Multiple-cycle extension of Study NEPA 08-18

N = 1286</td>
<td>See Study NEPA 08-18 above</td>
<td></td>
<td><u>Efficacy endpoints:</u> During the acute, delayed, and overall phases:
• CR
• No emesis
• No significant nausea</td>
<td>A total of 5969 total chemotherapy cycles were completed; 76% of patients completed at least 4 cycles.
<table>
<tr><th colspan="4">CR Rates: Overall Phase</th></tr>
<tr><th></th><th>AKYNZEO</th><th>Palonosetron</th><th>p Value</th></tr>
<tr><td>Cycle 1</td><td>74%</td><td>67%</td><td>0.001</td></tr>
<tr><td>Cycle 2</td><td>80%</td><td>67%</td><td>< 0.0001</td></tr>
<tr><td>Cycle 3</td><td>84%</td><td>70%</td><td>< 0.0001</td></tr>
<tr><td>Cycle 4</td><td>84%</td><td>75%</td><td>< 0.0001</td></tr>
<tr><th colspan="4">No Emesis</th></tr>
<tr><td>Cycle 1</td><td>80%</td><td>72%</td><td>< 0.001</td></tr>
<tr><td>Cycle 2</td><td>86%</td><td>74%</td><td>< 0.0001</td></tr>
<tr><td>Cycle 3</td><td>88%</td><td>77%</td><td>< 0.0001</td></tr>
<tr><td>Cycle 4</td><td>87%</td><td>79%</td><td>0.0003</td></tr>
<tr><th colspan="4">No Significant Nausea</th></tr>
<tr><td>Cycle 1</td><td>75%</td><td>69%</td><td>0.020</td></tr>
<tr><td>Cycle 2</td><td>77%</td><td>72%</td><td>0.018</td></tr>
<tr><td>Cycle 3</td><td>78%</td><td>73%</td><td>0.034</td></tr>
<tr><td>Cycle 4</td><td>80%</td><td>75%</td><td>0.042</td></tr>
</table>
AE rates across multiple cycles were similar between the two treatment groups.</td>
</tr>
<tr>
<td>AKYNZEO for the Prevention of CINV Over Repeated Cycles of Chemotherapy

Study NEPA 10-29

Gralla et al, 2014[18]</td>
<td>R, DB, DD, PG, MC, MN Phase III study

N = 413 adult patients with cancer scheduled to receive MEC or HEC

ITT efficacy analysis (n = 412)

Safety analysis (n = 412)</td>
<td><u>Inclusion:</u> Age ≥ 18 years; chemotherapy naïve; scheduled to receive multiple cycles of MEC or HEC for treatment of a malignant tumor; ECOG PS 0 to 2

<u>Exclusion:</u> Breast cancer and scheduled to receive A/C; scheduled to receive MEC or HEC on Days 2 to 5, or bone marrow or stem cell transplant; history of or predisposition to serious CV disease, cardiac conduction abnormalities, or torsades de pointes; scheduled to receive CYP3A4 inhibitors, inducers during the study or intake of strong/moderate inhibitors within 1 week of treatment or inducers within 4 weeks of treatment; previously received an NK_1 RA</td>
<td></td>
<td><u>Primary:</u> Safety (AEs; vital sign measurements; laboratory tests including CTnI; physical examination; ECG recordings including LVEF)

<u>Efficacy assessments:</u> CR during the acute, delayed, and overall phases; no significant nausea in the acute, delayed and overall phases</td>
<td>Safety:
• The most common treatment-emergent, drug-related AEs reported in the treatment groups were constipation (AKYNZEO, 3.6%; palonosetron/aprepitant, 1.0%) and headache (AKYNZEO, 1.0%; palonosetron/aprepitant, 1.0%).
• AE rates did not increase over multiple cycles, and the incidence, type, and frequency of treatment-emergent AEs was similar for both groups throughout the study.
• The treatment groups had comparable rates of patients who developed treatment-emergent ECG abnormalities.

Efficacy endpoints
• CR rates during the overall phase were high in both treatment groups over all 6 cycles of chemotherapy, ranging from 81% to 92% in the AKYNZEO group and from 76% to 88% in the palonosetron/aprepitant group. Although no formal statistical comparisons were performed, CR rates were numerically greater for patients receiving AKYNZEO during the overall phase and the delayed phase. CR rates were similar for the treatment groups during the acute phase.</td>
</tr>
</table>

Study	Design	Inclusion/Exclusion Criteria	Treatment	Endpoints	Results/Comments
Palonosetron PO vs IV Noninferiority Study					
Palonosetron Noninferiority Study Oral vs IV in HEC ***Study PALO 10-01***[1]	R, DB, DD, PG, MC, MN, single cycle N = 743 FAS (n = 738)	Inclusion: Adult, chemotherapy naïve, diagnosis of malignant solid tumor, scheduled to receive HEC Exclusion: Not reported		Primary: CR in the acute phase Other: Safety assessments	***Primary endpoint:*** Noninferiority of oral palonosetron vs IV palonosetron was demonstrated **Palonosetron IV** / **Palonosetron Oral** **FAS analysis** CR, acute phase: 86.2% / 89.4% Difference*: 3.21% *Noninferiority margin was set at 15% ***Safety:*** • The incidence of treatment-emergent AEs was similar in frequency and severity between treatment groups.
AKYNZEO: Supplementary Data					
Is the addition of an NK_1 receptor antagonist beneficial in patients receiving carboplatin? Supplementary data with NEPA, a fixed-dose combination of netupitant and palonosetron (oral presentation). ***Jordan et al, 2014***[56]	Post hoc analysis of a subset of patients receiving carboplatin in Study NEPA 10-29 N = 149	See Study NEPA 10-29 above		See Study NEPA 10-29 above	High no emesis rates were seen after a single dose of AKYNZEO + dexamethasone in this carboplatin subset. **AKYNZEO Carboplatin Subgroup** **CR, overall phase** Cycle 1 (N = 149): 80% Cycle 2 (N = 130): 91% Cycle 3 (N = 118): 92% Cycle 4 (N = 109): 94% **No emesis, overall phase** Cycle 1 (N = 149): 83% Cycle 2 (N = 130): 91% Cycle 3 (N = 118): 92% Cycle 4 (N = 109): 95% • This AKYNZEO dataset is the largest prospective report to date evaluating the contribution of a NK_1 receptor antagonist in preventing emesis in patients receiving carboplatin. • AKYNZEO was at least as effective as historical control rates for the aprepitant 3-drug regimen in both the cisplatin and carboplatin settings.

Study	Design	Inclusion/Exclusion Criteria	Treatment	Endpoints	Results/Comments
Do NK_1 Receptor Antagonists (RA) Contribute to Nausea Control? Evaluation of the Novel NEPA Fixed-dose Combination of NK_1 RA + 5-HT3 RA from Pivotal Trials (Oral Presentation). ***Schwartzberg et al, 2014***[57]	Post hoc analysis of nausea control in 2 pivotal trials: Studies NEPA 07-07 and NEPA 08-18	See Studies NEPA 07-07 and 08-18 above		See Studies NEPA 07-07 and 08-18 above	The addition of netupitant to palonosetron significantly improved overall prevention of nausea over palonosetron alone in patients receiving cisplatin or A/C.

NEPA 07-07: Cisplatin-Based HEC			
	AKYNZEO (n = 135)	**Palonosetron (n = 136)**	**OR (p value)**
No significant nausea			
Acute	99%	93%	4.74 (0.050)
Delayed	90%	81%	2.25 (0.027)
Overall	90%	79%	2.28 (0.021)
NEPA 08-18: A/C			
	AKYNZEO (n = 724)	**Palonosetron (n = 725)**	**OR (p value)**
No significant nausea			
Acute	87%	88%	0.95 (0.747)
Delayed	77%	71%	1.35 (0.014)
Overall	75%	69%	1.32 (0.020)

Proportion of Patients With No Impact on Daily Living Based on FLIE: NEPA 08-18 (A/C)

	AKYNZEO (n = 724)	**Palonosetron (n = 725)**	**p Value**
Nausea domain	72%	66%	0.015
Vomiting domain	90%	84%	0.001
Overall combined	79%	72%	0.005

- This analysis offers support that netupitant contributes to the prevention of nausea.
- The beneficial effect on nausea was greater with cisplatin than for A/C.

Study	Design	Inclusion/Exclusion Criteria	Treatment	Endpoints	Results/Comments
NEPA, A Fixed-dose Antiemetic Combination of Netupitant and Palonosetron: Results of Effectiveness in 407 Patients Receiving Cisplatin Plus Chemotherapy of Various Emetic Risk (Oral Presentation). ***Hesketh et al, 2014[14]***	Post hoc analysis of Study NEPA 07-07	See Study NEPA 07-07 above		Post hoc efficacy endpoints: During the acute, delayed, and overall phases: • CR • No significant nausea	This post-hoc analysis of one of the AKYNZEO pivotal trials was conducted to determine if emetic prevention following AKYNZEO administration differed based on the emetogenicity of the chemotherapy added to cisplatin. Treatment with AKYNZEO resulted in comparable and good CINV control in both risk categories in patients receiving cisplatin-based chemotherapy. **AKYNZEO Group**

	Cisplatin + Lower Risk (n = 265)	Cisplatin + Higher Risk (n = 142)
Complete response		
Acute	96%	94%
Delayed	91%	91%
Overall	89%	87%
No significant nausea		
Acute	96%	94%
Delayed	87%	87%
Overall	86%	85%

	Cisplatin + Lower Risk	Cisplatin + Higher Risk
Complete response		
AKYNZEO	89%	87%
Palonosetron	74%	81%
Aprepitant + ondansetron	88%	84%
No significant nausea		
AKYNZEO	86%	85%
Palonosetron	77%	84%
Aprepitant + ondansetron	89%	80%

Study	Design	Inclusion/Exclusion Criteria	Treatment	Endpoints	Results/Comments
Safety of NEPA, an Oral Fixed-dose Combination of Netupitant and Palonosetron: Pooled Data from the Phase 2/3 Clinical Program (Poster). ***Aapro et al, 2014[58]***	Pooled data analysis of 4 multinational, randomized, double-blind, clinical trials N = 3280 patients	Patients with cancer who participated in the Phase II/III AKYNZEO clinical program		AEs and ECG data	• AEs reported by ≥ 2% patients in any treatment group for Cycle 1 or all cycles were headache and constipation. • Most treatment-emergent AEs were of mild (27.4%, 900/3280) or moderate (24.5%, 803/3280) intensity, with < 10% of patients reporting severe events (9.8%, 320/3280). • The frequencies of mild, moderate, and severe events were similar across the treatment groups, with severe events reported in 10.4% (150/1442), 9.3% (149/1600), and 8.8% (21/238) of patients in the AKYNZEO, palonosetron, and aprepitant + ondansetron/palonosetron groups, respectively. • Cardiac AEs were reported at a similar rate in each treatment group: 12.1% (174/1442) in the AKYNZEO group, 8.7% (139/1600) in the palonosetron group, and 13.4% (32/238) in the aprepitant + ondansetron/palonosetron group. • Mean changes from baseline in ECG parameters assessed (HR, PR, QRS, QT, QTcB, and QTcF) were small and generally similar across treatment groups.

A/C = anthracycline/cyclophosphamide; AE = adverse event; CINV = chemotherapy-induced nausea and vomiting; CP = complete protection; CR = complete response; CTnI = cardiac troponin level; CV = cardiovascular; CYP = cytochrome P450; DB = double blind; DD = double dummy; Dex = dexamethasone; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FAS = full analysis set; FLIE = Functional Living Index–Emesis; HEC = highly emetogenic chemotherapy; HR = heart rate; ITT = intent to treat; IV = intravenous; KPS = Karnofsky Performance Status; LVEF = left ventricular ejection fraction; MC = multicenter; MEC = moderately emetogenic chemotherapy; MN = multinational; OR = odds ratio; PG = parallel group; PO = orally; PP = per protocol; PS = performance status; QTc = corrected QT interval; QTcB = Bazett corrected QT interval; QTcF = Fridericia corrected QT interval; R = randomized; RA = receptor antagonist

Summary of Evidence From Secondary Sources

There is currently no evidence from secondary sources for AKYNZEO.

SECTION IV:
Economic Value and Modeling Report
for AKYNZEO®
(netupitant/palonosetron) Capsules

ECONOMIC VALUE AND MODELING REPORT FOR AKYNZEO

Please contact Eisai Medical Information at 1-888-274-2378 for additional information.

SECTION V:
Other Supporting Evidence
for AKYNZEO®
(netupitant/palonosetron) Capsules

OTHER SUPPORTING EVIDENCE FOR AKYNZEO

There is currently no additional supporting evidence for AKYNZEO.

SECTION VI:
Supporting Information
for AKYNZEO®
(netupitant/palonosetron) Capsules

SUPPORTING INFORMATION FOR AKYNZEO

References

1. *AKYNZEO® (netupitant/palonosetron HCl) Capsules - Prescribing Information*. Woodcliff Lake, NJ: Eisai Inc.; October, 2014.
2. Hesketh PJ, Van Belle S, Aapro M, et al. Differential involvement of neurotransmitters through the time course of cisplatin-induced emesis as revealed by therapy with specific receptor antagonists. *Eur J Cancer.* 2003;39(8):1074-1080.
3. Rojas C, Slusher BS. Pharmacological mechanisms of 5-HT(3) and tachykinin NK(1) receptor antagonism to prevent chemotherapy-induced nausea and vomiting. *Eur J Pharmacol.* 2012;684(1-3):1-7.
4. National Cancer Comprehensive Network (NCCN). Clinical Practice Guidelines in Oncology. Antiemesis. v 1.2014. www.nccn.org. Accessed March 28, 2014.
5. Gomez DR, Liao KP, Giordano S, Nguyen H, Smith BD, Elting LS. Adherence to national guidelines for antiemesis prophylaxis in patients undergoing chemotherapy for lung cancer: a population-based study. *Cancer.* 2013;119(7):1428-1436.
6. Hesketh PJ. Chemotherapy-induced nausea and vomiting. *N Engl J Med.* 2008;358(23):2482-2494.
7. Roila F, Hesketh PJ, Herrstedt J. Prevention of chemotherapy- and radiotherapy-induced emesis: results of the 2004 Perugia International Antiemetic Consensus Conference. *Ann Oncol.* 2006;17(1):20-28.
8. Basch E, Prestrud AA, Hesketh PJ, et al. Antiemetics: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol.* 2011;29(31):4189-4198.
9. Multinational Association of Supportive Care in Cancer. MASCC/ESMO Antiemetic Guideline 2013. http://www.mascc.org/assets/documents/mascc_guidelines_english_2013.pdf. Accessed July 2, 2014.
10. Grunberg SM, Deuson RR, Mavros P, et al. Incidence of chemotherapy-induced nausea and emesis after modern antiemetics. *Cancer.* 2004;100(10):2261-2268.
11. Haiderali A, Menditto L, Good M, Teitelbaum A, Wegner J. Impact on daily functioning and indirect/direct costs associated with chemotherapy-induced nausea and vomiting (CINV) in a U.S. population. *Support Care Cancer.* 2011;19(6):843-851.
12. Stathis M, Pietra C, Rojas C, Slusher BS. Inhibition of substance P-mediated responses in NG108-15 cells by netupitant and palonosetron exhibit synergistic effects. *Eur J Pharmacol.* 2012;689(1-3):25-30.
13. Thomas AG, Stathis M, Rojas C, Slusher BS. Netupitant and palonosetron trigger NK receptor internalization in NG108-15 cells. *Exp Brain Res.* 2014.
14. Hesketh PJ, Gralla RJ, Rossi G, Palmas M, Giada Rizzi G. NEPA, a fixed-dose antiemetic combination of netupitant and palonosetron: Results of effectiveness in 407 patients receiving cisplatin plus chemotherapy of various emetic risk [oral presentation]. Presented at: MASCC/ISOO International Symposium on Supportive Care in Cancer; June 26-28, 2014; Miami, FL.
15. Aapro-Piacentini M, Rugo H, Rossi G, et al. A randomized Phase 3 study evaluating the efficacy and safety of NEPA, a fixed-dose combination of netupitant and palonosetron, for prevention of chemotherapy-induced nausea and vomiting following moderately emetogenic chemotherapy. *Ann Oncol.* 2014.
16. Cohen L, de Moor CA, Eisenberg P, Ming EE, Hu H. Chemotherapy-induced nausea and vomiting: incidence and impact on patient quality of life at community oncology settings. *Support Care Cancer.* 2007;15(5):497-503.
17. Bloechl-Daum B, Deuson RR, Mavros P, Hansen M, Herrstedt J. Delayed nausea and vomiting continue to reduce patients' quality of life after highly and moderately emetogenic chemotherapy despite antiemetic treatment. *J Clin Oncol.* 2006;24(27):4472-4478.
18. Gralla R, Bosnjak S, Hontsa A, et al. A Phase 3 study evaluating the safety and efficacy of NEPA, a fixed-dose combination of netupitant and palonosetron, for prevention of chemotherapy-induced nausea and vomiting over repeated cycles of chemotherapy. *Ann Oncol.* 2014.
19. de Boer-Dennert M, de Wit R, Schmitz PI, et al. Patient perceptions of the side-effects of chemotherapy: the influence of 5HT3 antagonists. *Br J Cancer.* 1997;76(8):1055-1061.
20. Burke TA, Wisniewski T, Ernst FR. Resource utilization and costs associated with chemotherapy-induced nausea and vomiting (CINV) following highly or moderately emetogenic chemotherapy administered in the US outpatient hospital setting. *Support Care Cancer.* 2011;19(1):131-140.

21. Mayer DK, Travers D, Wyss A, Leak A, Waller A. Why do patients with cancer visit emergency departments? Results of a 2008 population study in North Carolina. *J Clin Oncol.* 2011;29(19):2683-2688.

22. Feyer P, Jordan K. Update and new trends in antiemetic therapy: the continuing need for novel therapies. *Ann Oncol.* 2011;22(1):30-38.

23. Schwartzberg L, Szabo S, Gilmore J, et al. Likelihood of a subsequent chemotherapy-induced nausea and vomiting (CINV) event in patients receiving low, moderately or highly emetogenic chemotherapy (LEC/MEC/HEC). *Curr Med Res Opin.* 2011;27(4):837-845.

24. Darmani NA, Ray AP. Evidence for a re-evaluation of the neurochemical and anatomical bases of chemotherapy-induced vomiting. *Chem Rev.* 2009;109(7):3158-3199.

25. ASHP Therapeutic Guidelines on the Pharmacologic Management of Nausea and Vomiting in Adult and Pediatric Patients Receiving Chemotherapy or Radiation Therapy or Undergoing Surgery. *Am J Health Syst Pharm.* 1999;56(8):729-764.

26. Grunberg SM, Hesketh PJ. Control of chemotherapy-induced emesis. *N Engl J Med.* 1993;329(24):1790-1796.

27. Gregory RE, Ettinger DS. 5-HT3 receptor antagonists for the prevention of chemotherapy-induced nausea and vomiting. A comparison of their pharmacology and clinical efficacy. *Drugs.* 1998;55(2):173-189.

28. Geling O, Eichler HG. Should 5-hydroxytryptamine-3 receptor antagonists be administered beyond 24 hours after chemotherapy to prevent delayed emesis? Systematic re-evaluation of clinical evidence and drug cost implications. *J Clin Oncol.* 2005;23(6):1289-1294.

29. Hesketh PJ, Grunberg SM, Gralla RJ, et al. The oral neurokinin-1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting: a multinational, randomized, double-blind, placebo-controlled trial in patients receiving high-dose cisplatin--the Aprepitant Protocol 052 Study Group. *J Clin Oncol.* 2003;21(22):4112-4119.

30. Poli-Bigelli S, Rodrigues-Pereira J, Carides AD, et al. Addition of the neurokinin 1 receptor antagonist aprepitant to standard antiemetic therapy improves control of chemotherapy-induced nausea and vomiting. Results from a randomized, double-blind, placebo-controlled trial in Latin America. *Cancer.* 2003;97(12):3090-3098.

31. Sun CC, Bodurka DC, Weaver CB, et al. Rankings and symptom assessments of side effects from chemotherapy: insights from experienced patients with ovarian cancer. *Support Care Cancer.* 2005;13(4):219-227.

32. *Sancuso® (granisetron) Transdermal Patch - Prescribing Information*. Bedminster, NJ: ProStrakan Inc.; September 2014.

33. Bayo J, Fonseca PJ, Hernando S, et al. Chemotherapy-induced nausea and vomiting: pathophysiology and therapeutic principles. *Clin Transl Oncol.* 2012;14(6):413-422.

34. Saito R, Takano Y, Kamiya HO. Roles of substance P and NK(1) receptor in the brainstem in the development of emesis. *J Pharmacol Sci.* 2003;91(2):87-94.

35. Rossi G, Tilola SO, Rudengren C. A positron emission tomograpy (PET) study to assess the degree of neurokinin-1 (NK1) receptor occupancy in the human brain after single doses of netupitant to healthy male subjects [poster]. Presented at: American Society of Clinical Oncology; June 1 - 5, 2012; Chicago, IL.

36. *Emend® (aprepitant) Capsules for Oral Use* - Prescribing Information. Whitehouse Station, NJ: Merck & Co., Inc.; August, 2014.

37. *Emend® (fosaprepitant dimeglumine) for Injection - Prescribing Information*. Whitehouse Station, NJ: Merck & Co., Inc.; August, 2014.

38. *ALOXI® (palonosetron HCl) Injection for Intravenous Use - Prescribing Information.* Woodcliff Lake, NJ: Eisai Inc.; September, 2014.

39. Rojas C, Stathis M, Thomas AG, et al. Palonosetron exhibits unique molecular interactions with the 5-HT3 receptor. *Anesth Analg.* 2008;107(2):469-478.

40. *Zofran® (ondansetron HCl) Tablets, Zofran ODT® (ondansetron) Orally Disintegrating Tablets, and Zofran® (ondansetron HCl) Oral Solution - Prescribing Information.* Research Triangle Park, NC: GlaxoSmithKline; September 2014.

41. *Granisetron Hydrochloride Tablets- Prescribing Information*. Sellersville, PA: Teva Pharmaceuticals USA; August, 2014.

42. Wong EH, Clark R, Leung E, et al. The interaction of RS 25259-197, a potent and selective antagonist, with 5-HT3 receptors, in vitro. *Br J Pharmacol.* 1995;114(4):851-859.
43. Yang LP, Scott LJ. Palonosetron: in the prevention of nausea and vomiting. *Drugs.* 2009;69(16):2257-2278.
44. Rojas C, Thomas AG, Alt J, et al. Palonosetron triggers 5-HT(3) receptor internalization and causes prolonged inhibition of receptor function. *Eur J Pharmacol.* 2010;626(2-3):193-199.
45. US Food and Drug Administration. Drugs @ FDA. Aloxi. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Overview&DrugName=ALOXI. Accessed June 6, 2014.
46. *Ondansetron Injection, USP - Prescribing Information*. Lake Forest, IL: Hospira, Inc.; September, 2014.
47. *Zuplenz® (ondansetron) Oral Dissolving Film - Prescribing Information.* Cary, NC: Praelia Pharmaceuticals, Inc.; September, 2014.
48. *Anzemet® (dolasetron mesylate) Tablets - Prescribing Information*. Bridgewater, NJ: sanofi-aventis U.S. LLC; September, 2014.
49. *Granisetron Hydrochloride Injection - Prescribing Information*. Sellersville, PA: Teva Pharmaceuticals USA; August, 2014.
50. *Granisol™ (granisetron HCl) Oral Solution - Prescribing Information*. Califon, NJ: PediatRx. November, 2010.
51. Hesketh PJ, Rossi G, Rizzi G, et al. Efficacy and safety of NEPA, an oral combination of netupitant and palonosetron, for prevention of chemotherapy-induced nausea and vomiting following highly emetogenic chemotherapy: A randomized dose-ranging pivotal study. *Ann Oncol.* 2014.
52. Aapro A, Karthaus M, Schwartzberg L, et al. Phase 3 study of NEPA, a fixed-dose combination of netupitant and palonosetron, for prevention of chemotherapy-induced nausea and vomiting during repeated moderately emetogenic chemotherapy (MEC) cycles [oral presentation]. Presented at: ASCO Annual Meeting; May 30-June 2, 2014; Chicago, IL.
53. Gralla R, Rossi G, Rizzi G, et al. Improved control of nausea and vomiting (CINV) with a fixed-dose combination of netupitant and palonosetron (NEPA) following highly emetogenic chemotherapy (HEC): Results from a pivotal study [poster]. Presented at: European Cancer Congress; September 27 - October 1, 2013; Amsterdam.
54. Aapro M, Rossi G, Rizzi G, et al. Efficacy and safety of NEPA, a fixed-dose combination of netupitant and palonosetron in preventing chemotherapy-induced nausea and vomiting (CINV) in patients receiving moderately emetogenic chemotherapy (MEC) [poster]. Presented at: European Cancer Congress; September 27 - October 1, 2013; Amsterdam.
55. Gralla RJ, Bosnjak SM, Balser C, et al. Prevention of chemotherapy-induced nausea and vomiting (CINV) over repeated chemotherapy cycles: Results of a phase 3 trial of NEPA, a fixed-dose combination of netupitant and palonosetron [poster]. Presented at: European Cancer Congress; September 27 - October 1, 2013; Amsterdam.
56. Jordan K, Gralla R, Rossi G, Borroni ME, Rizzi G. Is the addition of an NK1 receptor antagonist beneficial in patients receiving carboplatin? Supplementary data with NEPA, a fixed-dose combination of netupitant and palonosetron [oral presentation]. Presented at: MASCC/ISOO International Symposium on Supportive Care in Cancer; June 26 - 28, 2014; Miami, FL.
57. Schwartzberg L, Aapro M, Hesketh P, et al. Do NK1 Receptor Antagonists (RA) Contribute to Nausea Control? Evaluation of the Novel NEPA Fixed-dose Combination of NK1 RA + 5-HT3 RA from Pivotal Trials [Oral Presentation]. Presented at: MASCC/ISOO International Symposium on Supportive Care in Cancer; June 26-28, 2014; Miama, FL.
58. Aapro M, Hesketh PJ, Jordan K, et al. Safety of NEPA, an oral fixed-dose combination of netupitant and palonosetron: Pooled data from the Phase 2/3 clinical program [poster]. Presented at: MASCC/ISOO International Symposium on Supportive Care in Cancer; June 26-28, 2014; Miami, FL.

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

AKYNZEO Prescribing Information

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-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-HT_3 receptor antagonists (5.1)
- Serotonin syndrome has been reported with 5-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

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%

AMCP Dossier for AKYNZEO® – PROPRIETARY & CONFIDENTIAL. DO NOT COPY OR DISTRIBUTE.

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,

AMCP Dossier for AKYNZEO® – PROPRIETARY & CONFIDENTIAL. DO NOT COPY OR DISTRIBUTE.

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.

AMCP Dossier for AKYNZEO® – PROPRIETARY & CONFIDENTIAL. DO NOT COPY OR DISTRIBUTE.

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)]*.

AMCP Dossier for AKYNZEO® – PROPRIETARY & CONFIDENTIAL. DO NOT COPY OR DISTRIBUTE.

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

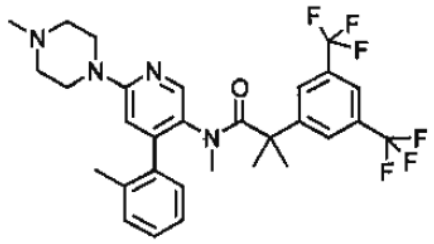
No specific information is available on the treatment of overdosage with AKYNZEO. In the event of overdose, AKYNZEO should be discontinued and general supportive treatment and monitoring should be provided. Because of the antiemetic activity of AKYNZEO, drug-induced emesis may not be effective. Dialysis 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.

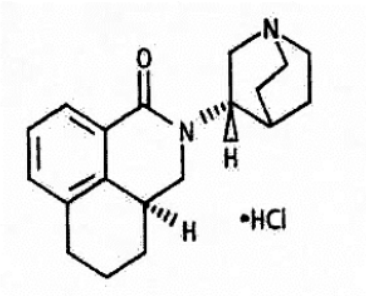
11 DESCRIPTION

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:



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.

AMCP Dossier for AKYNZEO® – PROPRIETARY & CONFIDENTIAL. DO NOT COPY OR DISTRIBUTE.

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

AMCP Dossier for AKYNZEO® – PROPRIETARY & CONFIDENTIAL. DO NOT COPY OR DISTRIBUTE.

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.

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.

AMCP Dossier for AKYNZEO® – PROPRIETARY & CONFIDENTIAL. DO NOT COPY OR DISTRIBUTE.

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.

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.

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

AMCP Dossier for AKYNZEO® – PROPRIETARY & CONFIDENTIAL. DO NOT COPY OR DISTRIBUTE.

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%).

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.

AMCP Dossier for AKYNZEO® – PROPRIETARY & CONFIDENTIAL. DO NOT COPY OR DISTRIBUTE.

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%).

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

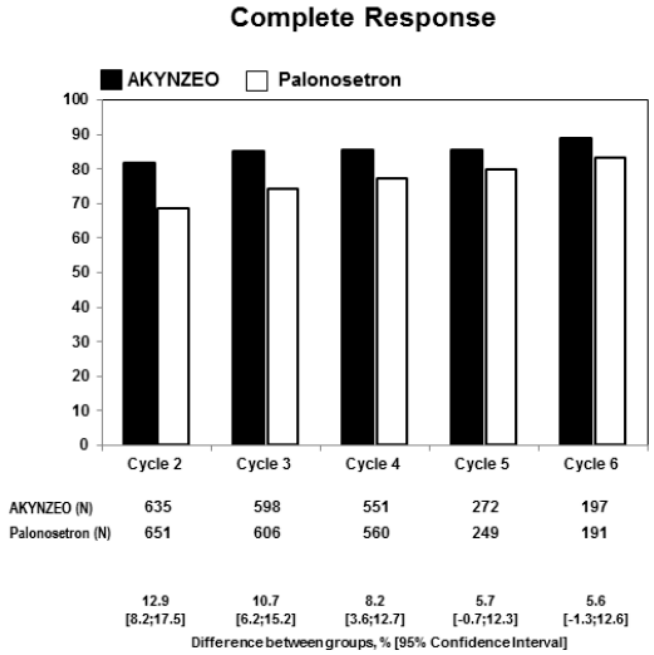
*p-value from Cochran-Mantel-Haenszel test, stratified by age class and region.
‡Acute phase: 0 to 24 hours after anthracycline and cyclophosphamide regimen.
†Delayed phase: 25 to 120 hours after anthracycline and cyclophosphamide regimen.
§Overall: 0 to 120 hours after anthracycline and cyclophosphamide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

AMCP Dossier for AKYNZEO® – PROPRIETARY & CONFIDENTIAL. DO NOT COPY OR DISTRIBUTE.

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.

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.	