Formulary Drug Reviews

Netupitant/Palonosetron

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Generic Name:	Netupitant/Palonosetron
Proprietary Name:	Akynzeo (Eisai Inc)
Approval Rating:	1S
Therapeutic Class:	5-HT ₃ receptor antagonists; Antiemetic agents; NK ₁ receptor antagonists
Similar Drugs:	Aprepitant, Dolasetron, Fosaprepitant, Granisetron, Ondansetron, Palonosetron
Sound- or Look-Alike Names:	Aprepitant, Dolasetron, Fosaprepitant, Granisetron, Ondansetron, Palonosetron

INDICATIONS

Netupitant/palonosetron, in a fixed-dose combination, is approved for the prevention of acute and delayed nausea and vomiting associated with initial and repeat doses of chemotherapy, including, but not limited to, highly emetogenic chemotherapy (HEC) regimens.^{1,2} See **Table 1** for a comparison of US Food and Drug Administration (FDA)–approved

indications for 5-HT₃ antagonists and neurokinin 1 (NK₁) inhibitors.^{1,3–14}

CLINICAL PHARMACOLOGY

Chemotherapy-induced nausea and vomiting (CINV) is a commonly occurring adverse event following use of chemotherapeutic regimens for treatment of cancers.¹⁵ Multiple patient risk factors (eg, age, gender, alcohol consumption) have been identified along with the emetogenic potential of individual or combination chemotherapeutic agents.^{15,16} The exact mechanism is unclear, but acute-phase nausea is potentially due to the release of serotonin (5-HT) by enterochromaffin cells in the gastrointestinal (GI) tract.^{1,15} The delayed phase is thought to be due to substance P activation of NK₁ receptors.¹ Activation of NK₁ receptors, both centrally and peripherally, by substance P is involved in multiple physiologic pathways, including pain and migraine regulation, nausea and vomiting, mood and anxiety levels, alcoholism, and inflammatory conditions of the GI tract.^{17,18}

In vitro models show that netupitant inhibits the action of substance P at the human NK₁ receptor in a concentration-dependent manner, and a human

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Table 1. FDA-approved indications for 5-HT₃ antagonists and NK₁ inhibitors^{1,3-14}

		Prevention of acute and delayed CINV with HEC	Prevention of acute CINV with HEC	Prevention of acute CINV and delayed with MEC therapy	Prevention of CINV with MEC therapy	Prevention of PONV	Prevention of N/V after irradiation
Netupitant/ Palonosetron	Oral capsule	X					
Aprepitant	Oral tablet	X			X	X	
Fosaprepitant	Injectable solution	X			X		
Dolasetron	Injectable solution Oral tablet				X	X	
Granisetron	Injectable solution Oral tablet Oral solution Transdermal patch		X X X X		X X X X		X X
Ondansetron	Injectable solution Oral tablet ODT Oral solution ODF		X X X X X		X X X X X	X X X X X	X X X X X
Palonosetron	Injectable solution		X	X	X	X	

Note: CINV = chemotherapy-induced nausea and vomiting; MEC = moderately emetogenic chemotherapy; N/V = nausea and vomiting; ODF = orally disintegrating film; ODT = orally disintegrating tablet; PONV = postoperative nausea and vomiting.

positron emission tomography study showed that netupitant is able to cross the blood-brain barrier.^{17,18} Netupitant is present in the frontal and occipital cortex, the striatum, the anterior cingulate, and the lateral and medial temporal cortex.¹⁸ Palonosetron is a 5-HT₃ receptor antagonist that inhibits the serotonin secreted from stimulation by chemotherapy.¹ An in vitro model showed that the combination of netupitant and palonosetron inhibited activation of NK₁ receptors by substance P in a synergistic manner; neither chemical alone inhibited activation at the synergistic concentrations studied.¹⁹ Netupitant and palonosetron had no action at NK₂ or NK₃ receptors.¹⁹

PHARMACOKINETICS

Combinations of netupitant 200 to 600 mg and palonosetron 0.5 to 1.5 mg have total exposure (area under the curve [AUC]) and mean maximum concentration (C_{max}) best characterized by a linear pharmacokinetic model.²⁰ Between-subject variability is between 42% and 56% for netupitant 200 to 600 mg and between 20% and 29% for palonosetron 0.5 to 1.5 mg.²⁰ At the doses studied, netupitant and palonosetron have no effect on the pharmacokinetic parameters of each other.^{1,21}

Following oral administration of netupitant and palonosetron in healthy subjects, the time to maximum concentration (T_{max}) is about 5 hours for both drugs.¹ Additionally, coadministration with food, presence of cancer, or subsequent administration of chemotherapy have no effect on the pharmacokinetic parameters of netupitant and palonosetron.¹

Netupitant monotherapy has linear pharmacokinetics in regard to C_{max} and AUC in single doses ranging from 100 to 450 mg.¹⁸ After oral administration of netupitant, T_{max} is about 5 hours.^{1,18} Netupitant and its metabolites (M1, M2, and M3) are highly bound in plasma proteins (99.5% netupitant, 97.5% metabolites).¹ Netupitant undergoes significant metabolism to a multitude of metabolites via both phase 1 and phase 2 processes. The primary metabolites M1, M2, and M3 account for 29%, 14%, and 33%, respectively, of the circulating exposure to netupitant; these metabolites are active in animal models.^{1,18} The approximate half-life after a single dose of netupitant in cancer patients is 80 hours.¹ Netupitant 300 mg has a long duration of receptor occupancy at 96 hours, which contributes to its duration of effect.¹⁸

Following oral administration of radiolabeled netupitant, half of the radioactivity is recovered in feces and urine 120 hours post dose; 70% and 4% of

the drug are recovered in feces and urine, respectively, by 336 hours; and 86.5% and 4.8% of the drug are recovered in feces and urine, respectively, by 30 days post dose. Radioactivity is recovered primarily as metabolites.¹⁸

Palonosetron monotherapy (3 to 80 mcg/kg in healthy subjects) demonstrates dose-proportional pharmacokinetics. After oral administration, bioavailability is 97%. Palonosetron is approximately 62% bound to plasma proteins. Primary metabolism is via cytochrome P450 (CYP-450) 2D6 and, to a lesser extent, 3A4 and 1A2. The half-life of palonosetron in patients with cancer is 48 hours.¹

The pharmacokinetic parameters for the 5-HT₃ antagonists and NK₁ inhibitors are compared in Table 2.^{1,3-14}

COMPARATIVE EFFICACY

Indication: Prevention of Chemotherapy-Induced Nausea and Vomiting

Guidelines

Guideline: European Society of Medical Oncology/Multinational Association of Supportive Care in Cancer (ESMO/MASCC) Guidelines Working Group; guideline update for MASCC and ESMO in the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting

Reference: Roila F, et al, 2010¹⁶

Comments: In patients undergoing HEC, prevention of acute nausea and vomiting should include a 5-HT₃ antagonist, dexamethasone, and aprepitant. All patients receiving cisplatin should receive antiemetic therapy to prevent delayed nausea and vomiting; a recommended treatment for both acute and delayed nausea and vomiting is a 5-HT₃ antagonist plus dexamethasone plus aprepitant on day 1, followed by aprepitant plus dexamethasone on days 2 to 3 and dexamethasone alone on day 4. The guidelines recommend NK₁ antagonists as a class; at the time these guidelines were published, aprepitant was the only approved NK₁ antagonist. In patients undergoing treatment with moderately emetogenic chemotherapy (MEC) containing anthracycline/cyclophosphamide, a 5-HT₃ antagonist plus dexamethasone plus aprepitant is recommended on day 1 followed by aprepitant on days 2 to 3. For MEC not containing anthracycline/cyclophosphamide, palonosetron plus dexamethasone on day 1 followed by dexamethasone on days 2 to 3

Table 2. Pharmacokinetic parameters for 5-HT₃ antagonists and NK₁ inhibitors^{1,3-14}

Agent	Dosage form	T _{max}	t _{1/2}	Metabolism	Excretion	Dose adjustments
Netupitant/ Palonosetron	Oral capsule	5 h; 5 h	96 h; 44 h	CYP3A4, CYP2C9, CYP2D6; CYP2D6, CYP3A4, CYP1A2	Feces as metabolites; urine as metabolites	No adjustments
Dolasetron (hydrodolasetron)	Injectable solution Oral tablet	36 min 1 h	7.3 h 8.1 h	CYP2D6, CYP3A	Urine 53% to 61% unchanged	No adjustments
Aprepitant	Oral tablet	3 to 4 h	9 to 13 h	CYP3A4, CYP1A2, CYP2C19	Urine 57%, feces 45%	No adjustments
Fosaprepitant	Injectable solution	20 min	9 to 13 h			
Granisetron	Injectable solution Oral tablet Oral solution Transdermal patch	— — — 48 h	4.9 to 8.9 h 6.2 h 6.2 h —	CYP3A	Urine 12% unchanged	No adjustments
Ondansetron	Injectable solution Oral tablet ODT Oral solution ODF	10 min (IV); 41 min (IM) 1.7 to 2.2 h 1.7 to 2.2 h 1.7 to 2.2 h 1.7 h	3.5 to 5.5 h 3.1 to 6.2 h 3.1 to 6.2 h 3.1 to 6.2 h 4.5 to 5.4 h	CYP1A2, CYP2D6, CYP3A4	Urine 5% unchanged	Severe hepatic impairment
Palonosetron	Injectable solution	5 min	40 h	CYP2D6, CYP3A4, CYP1A2	Urine as metabolites	No adjustments

Note: h = hours; IM = intramuscular; IV = intravenous; min = minutes; ODF = orally disintegrating film; ODT = orally disintegrating tablet; t_{1/2} = terminal half-life.

is recommended. No difference has been reported between oral and parenteral dosage forms. These guidelines were published prior to approval of the netupitant/palonosetron combination.

Studies

Drug: Netupitant/Palonosetron plus Dexamethasone vs Palonosetron plus Dexamethasone

Reference: Aapro M, et al, 2014²²

Study Design: Randomized, double-blind, double-dummy, active-controlled, multicenter study

Study Funding: Helsinn Healthcare, SA

Patients: 1,450 patients 18 years and older with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 who were naive to chemotherapy for a solid tumor and scheduled to receive their first course of an anthracycline/cyclophosphamide-containing MEC regimen. Key exclusion criteria included planned HEC on days 1 to 5 or additional MEC on days 2 to 5, radiation therapy, or bone marrow or stem-cell transplant. Patients could not use medications with known emetogenic efficacy within 24 hours prior to day 1 and were excluded if they experienced vomiting, retching, or mild nausea within 24 hours prior to day 1. Additional exclusion criteria included a history of cardiovascular disease, conduction abnormalities (except incomplete right bundle branch block), use of CYP3A4 inducers within 4 weeks, use of strong or moderate CYP3A4 inhibitors within 1 week, and concomitant use of inducers or substrates. Median age was 54 years, 98% were women, and approximately 80% were White; approximately 97.5% had breast cancer, approximately 99% had an ECOG performance status of 0 or 1, and 63.7% to 68% received doxorubicin.

Intervention: Patients were randomized 1:1 to receive netupitant 300 mg/palonosetron 0.5 mg plus dexamethasone 12 mg or palonosetron 0.5 mg plus dexamethasone 20 mg on day 1 prior to chemotherapy. Netupitant/palonosetron or palonosetron was administered 60 minutes prior to chemotherapy, and dexamethasone was administered 30 minutes prior to chemotherapy. Chemotherapeutic regimens contained cyclophosphamide 500 to 1,500 mg/m² and either doxorubicin (at least 40 mg/m²) or epirubicin (at least 60 mg/m²). Investigators were provided metoclopramide tablets as rescue treatment, but could use alternative

rescue treatment at their own discretion (excluding 5-HT₃ antagonists, NK₁ antagonists). Use of rescue medication was considered treatment failure.

Results

Primary Endpoint(s)

- Proportion of patients with a complete response (no emesis, no rescue medication) during the delayed phase (25 to 120 hours) was 76.9% with netupitant/palonosetron and 69.5% with palonosetron ($P = .001$). Number needed to treat (NNT) with netupitant/palonosetron compared with palonosetron alone was 13.5.

Secondary Endpoint(s)

- Proportion of patients with a complete response during the acute phase (0 to 24 hours) was 88.4% with netupitant/palonosetron and 85% with palonosetron ($P = .047$; NNT = 29.4).
- Proportion of patients with a complete response overall (0 to 120 hours) was 74.3% with netupitant/palonosetron and 66.6% with palonosetron ($P = .001$; NNT = 13).
- Proportion of patients with complete protection (complete response without significant nausea) with netupitant/palonosetron and palonosetron during the acute phase (82.3% vs 81.1%; $P = .528$), delayed phase (67.3% vs 60.3%; $P = .005$; NNT = 14.3), and overall period (63.8% vs 57.9%; $P = .02$; NNT = 17).
- Proportion of patients with no significant nausea (visual analog score less than 25 mm) with netupitant/palonosetron and palonosetron during the acute phase (87.3% vs 87.9%; $P = 0.747$), delayed phase (76.9% vs 71.3%; $P = .014$; NNT = 17.9), and overall period (74.6% vs 69.1%; $P = .02$; NNT = 18.2).
- Proportion of patients with no emesis with netupitant/palonosetron and palonosetron during the acute phase (90.9% vs 87.3%; $P = .025$; NNT = 27.8), delayed phase (81.8% vs 75.6%; $P = .004$; NNT = 16.1), and overall period (79.8% vs 72.1%; $P < .001$; NNT = 13).

Endpoint(s)

- Proportion of patients for whom nausea and vomiting had no impact on daily life based on Functional Living Index-Emesis (FLIE) questionnaire score was 78.5% with netupitant/palonosetron and 72.1% with palonosetron ($P = .005$; NNT = 15.6).
- The most commonly reported adverse events were headache and constipation and were reported at similar rates between groups.

Comments: This was a phase 3 pivotal trial. The trial showed an improvement in nausea and vomiting over palonosetron in women undergoing their first treatment for breast cancer with a combination of cyclophosphamide and either doxorubicin or epirubicin. This study does not show an effect on anticipatory nausea. Stratification was based on region and age (younger than 55 years [51.2%] or 55 years and older [48.8%]). Patients were eligible to enter an extension trial for repeat consecutive cycles of chemotherapy. A safety trial reported by Gralla and colleagues randomized 413 patients (1,961 chemotherapy cycles; 76% MEC and 24% HEC) 3:1 to receive either palonosetron plus netupitant or palonosetron plus aprepitant.²³ A total of 75% of patients completed at least 4 cycles. Over multiple cycles, 10.1% of patients experienced treatment-related adverse events in the netupitant arm, and 5.8% experienced treatment-related adverse events in the aprepitant arm (number needed to harm [NNH] of 23); the most commonly reported adverse event of multiple cycles was constipation (3.6% with netupitant; 1% with aprepitant). Efficacy (complete response rates) was sustained over 6 cycles of chemotherapy and was similar between the 2 treatment arms. The safety study excluded patients with breast cancer receiving anthracycline/cyclophosphamide-containing MEC.

Limitations: The study did not include a significant proportion of male subjects because the majority of patients had been diagnosed with breast cancer.

Drug: Netupitant/Palonosetron plus Dexamethasone vs Palonosetron plus Dexamethasone vs Aprepitant plus Ondansetron plus Dexamethasone

Reference: Hesketh PJ, et al, 2014²⁴

Study Design: Randomized, double-blind, double-dummy, active-controlled, multicenter study

Study Funding: Helsinn Healthcare, SA

Patients: 694 patients 18 years and older with a Karnofsky performance score of at least 70% and who were naive to chemotherapy and scheduled to receive their first course of cisplatin (50 mg/m² or greater) alone or in combination for the treatment of a malignant tumor. Key exclusion criteria included planned HEC or MEC on days 2 to 5, moderately or highly emetogenic radiotherapy, or bone marrow or stem-cell transplant. Patients

were not allowed to use medications with known emetogenic efficacy within 24 hours prior to day 1 or systemic corticosteroids within 72 hours of day 1. Patients were also excluded if they experienced vomiting, retching, or mild nausea within 24 hours prior to day 1. Additional exclusion criteria included a history of or predisposition to cardiovascular disease and conduction abnormalities (except incomplete right bundle branch block). Use of CYP3A4 inducers within 4 weeks, use of strong or moderate CYP3A4 inhibitors within 1 week, and concomitant use of inducers or substrates were prohibited. Median age was 55 years and approximately 57% were men; approximately 57% did not use alcohol, approximately 50% had lung, head, and neck cancers; approximately 60% had a Karnofsky performance score of 90%; approximately 50% received cisplatin plus a low emetogenic therapy; and approximately 35% received cisplatin plus MEC or HEC.

Intervention: Patients were evenly randomized to 1 of 5 of the following treatment arms: placebo plus palonosetron 0.5 mg plus oral dexamethasone 20 mg on day 1, followed by oral dexamethasone 8 mg twice daily on days 2 to 4 (palonosetron 0.5 mg alone); oral netupitant 100, 200, or 300 mg plus palonosetron 0.5 mg plus dexamethasone 12 mg on day 1, followed by dexamethasone 4 mg twice daily on days 2 to 4; or oral aprepitant 125 mg plus IV ondansetron 32 mg plus oral dexamethasone 12 mg on day 1 followed by oral aprepitant 80 mg daily and dexamethasone 4 mg twice daily for days 2 to 3, and then followed by oral dexamethasone 4 mg twice daily on day 4 (aprepitant plus ondansetron). Investigators could use rescue treatment with the exclusion of 5-HT₃ antagonists or NK₁ antagonists. Use of rescue medication was considered treatment failure.

Results

Primary Endpoint(s)

- Proportion of patients with a complete response during the overall period (0 to 120 hours) was 87.4% ($P \leq .05$) with netupitant 100 mg plus palonosetron, 87.6% ($P \leq .05$) with netupitant 200 mg plus palonosetron, 89.6% ($P \leq .01$) with netupitant 300 mg plus palonosetron, 86.6% ($P \leq .05$) with aprepitant plus ondansetron, and 76.5% with palonosetron 0.5 mg alone. NNT

with netupitant 300 mg plus palonosetron versus palonosetron 0.5 mg alone was 7.6.

Secondary Endpoint(s)

- Proportion of patients with a complete response during the delayed phase (25 to 120 hours) was 90.4% ($P \leq .05$) with netupitant 100 mg plus palonosetron, 91.2% ($P \leq .05$) with netupitant 200 mg plus palonosetron, 90.4% ($P \leq .05$) with netupitant 300 mg plus palonosetron, 88.8% ($P \leq .05$) with aprepitant plus ondansetron, and 80.1% with palonosetron 0.5 mg alone. NNT for netupitant 300 mg plus palonosetron versus palonosetron 0.5 mg alone was 9.7.
- Proportion of patients with a complete response during the acute phase (0 to 24 hours) was 93.3% with netupitant 100 mg plus palonosetron, 92.7% with netupitant 200 mg plus palonosetron, 98.5% ($P \leq .05$) with netupitant 300 mg plus palonosetron, 94.8% with aprepitant plus ondansetron, and 89.7% with palonosetron 0.5 mg alone. NNT with netupitant 300 mg plus palonosetron versus palonosetron 0.5 mg alone was 11.4.

- Additional results are presented in Table 3.

Endpoint(s)

- The most common adverse events in all palonosetron arms were hiccups, headache, and leukocytosis.

Comments: This was a phase 2 pivotal, dose-ranging trial. Stratification was based on gender, and subgroup analysis suggested that netupitant plus palonosetron elicited more of a benefit in women than in men. The study was not powered to show a difference between aprepitant and netupitant arms, and all analyses of aprepitant compared with the palonosetron-only arm were post hoc.

Limitations: The trial was not conducted at US sites.

CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS

The contraindications, warnings, precautions, and use in special populations for the 5-HT₃ antagonists and NK₁ inhibitors are summarized in Tables 4 and 5.^{1,3-14}

Contraindications

No contraindications are listed in the prescribing information.¹ Hypersensitivity to active ingredient

Table 3. Proportion of patients achieving no emesis or no significant nausea over study period²⁴

	Palonosetron 0.5 mg alone	Netupitant 100 mg plus palonosetron	Netupitant 200 mg plus palonosetron	Netupitant 300 mg plus palonosetron	Aprepitant plus ondansetron
No emesis (0 to 24 h)	89.7%	93.3%	92.7%	98.5% ($P < .01$; NNT = 11.4)	94.8%
No emesis (25 to 120 h)	80.1%	90.4%	91.2%	91.9% ($P < .01$; NNT = 8.5)	89.6% ($P \leq .05$)
No emesis (0 to 120 h)	76.5%	87.4% ($P \leq .05$)	87.6% ($P \leq .05$)	91.1% ($P \leq .01$; NNT = 6.8)	87.3% ($P \leq .05$)
No significant nausea (0 to 24 h)	93.4%	94.1%	94.2%	98.5% ($P \leq .05$; NNT = 19.6)	94%
No significant nausea (25 to 120 h)	80.9%	81.5%	89.8% ($P \leq .05$)	90.4% ($P \leq .01$; NNT = 10.5)	88.1%
No significant nausea (0 to 120 h)	79.4%	80%	86.1%	89.6% ($P \leq .05$; NNT = 9.8)	85.8%
Complete protection (0 to 24 h)	87.5%	89.6%	88.3%	97% ($P \leq .05$; NNT = 10.5)	89.6%
Complete protection (25 to 120 h)	73.5%	80%	87.6% ($P \leq .01$)	84.4% ($P \leq .05$; NNT = 9.2)	82.1%
Complete protection (0 to 120 h)	69.9%	76.3%	80.3% ($P \leq .05$)	83% ($P \leq .01$; NNT = 7.6)	78.4%

Note: P values are comparison with palonosetron 0.5 mg without an NK₁ antagonist group. h = hours; NNT = number needed to treat compared with palonosetron alone.

Table 4. Contraindications, warnings, and precautions for 5-HT₃ antagonists and NK₁ inhibitors^{1,3-14}

	Netupitant/ Palonosetron	Dolasetron		Palonosetron		Ondansetron				Granisetron				Aprepitant		Fosaprepitant		
	OC	IS	OT	IS	IS	IS	OT	ODT	OS	ODF	IS	OT	OS	TDS	OT	IS		
Contraindications																		
Hypersensitivity	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
CINV	X																	
Concomitant use with apomorphine					X		X	X	X	X								
Administration with pimozide, terfenadine, astemizole, or cisapride																X	X	
Warnings and precautions																		
Hypersensitivity	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Serotonin syndrome	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
QT c prolongation		X	X		X	X	X	X	X	X	X	X	X	X				
PR/QRS prolongation		X	X															
Not a substitute for gastric suction					X	X	X	X	X	X	X	X	X	X				
Masked ileus					X													
Skin reactions						X												
Sunlight exposure						X												
Administration with CYP3A4																	X	X
Administration with warfarin																	X	X
Administration with hormonal contraceptives																	X	X
Severe hepatic failure																	X	
Chronic use																	X	X

Note: CINV = chemotherapy-induced nausea and vomiting; IS = injectable solution; OC = oral capsule; ODF = orally disintegrating film; ODT = orally disintegrating tablet; OS = oral solution; OT = oral tablet, PONV = postoperative nausea and vomiting; TDS = transdermal delivery system.

Table 5. Use of 5-HT₃ antagonists and NK₁ inhibitors in special populations^{1,3-14}

	Netupitant/ Palonosetron	Dolasetron	Palonosetron	Ondansetron	Granisetron	Aprepitant	Fosaprepitant
Pregnancy	Category C	Category B	Category B	Category B	Category B	Category B	Category B
Breast-feeding	Discontinue	Discontinue	Discontinue	Use caution	Use caution	Discontinue	Discontinue
Pediatric	Not approved	2 years and older	1 month and older for CINV	IS: 1 month and older for PONV; 6 months and older for CINV OT, ODT, OS, ODF: 4 years and older for CINV	IS: 2 years and older CINV OT, OS, TDS; Not approved	Not approved	Not approved
Elderly	No adjustment recommended	No adjustment recommended	No adjustment recommended	No adjustment recommended	No adjustment recommended	No adjustment recommended	No adjustment recommended
Hepatic impairment	No adjustment for mild to moderate impairment; avoid in severe impairment	No adjustment recommended	No adjustment recommended	Severe impairment; maximum of 8 mg/day	No adjustment recommended	No adjustment for mild to moderate impairment; use caution in severe impairment	No adjustment for mild to moderate impairment; use caution in severe impairment
Renal impairment	No adjustment for mild to moderate impairment; avoid in severe impairment	No adjustment recommended	No adjustment recommended	No adjustment recommended	No adjustment recommended	No adjustment recommended	No adjustment recommended

Note: CINV = chemotherapy-induced nausea and vomiting; IS = injectable solution; OC = oral capsule; ODF = orally disintegrating film; ODT = orally disintegrating tablet; OS = oral solution; OT = oral tablet; PONV = postoperative nausea and vomiting; TDS = transdermal delivery system.

or any inactive ingredients (eg, microcrystalline cellulose, sucrose fatty acid esters, povidone K-30, croscarmellose sodium, silicon dioxide, sodium stearyl fumarate, magnesium stearate, monoglycerides and diglycerides of capryl/capric acid, glycerin, polyglyceryl oleate, butylated hydroxyanisole, gelatin, sorbitol, titanium dioxide, yellow iron oxide, and red iron oxide; trace amounts of medium-chain triglycerides, lecithin, and denatured ethanol) should be considered a contraindication to therapy.¹

Warnings and Precautions

Hypersensitivity reactions have been reported in patients treated with 5-HT₃ receptor antagonists. These reactions were reported in patients with and without known hypersensitivity to other 5-HT₃ receptor antagonists.¹

Serotonin syndrome, sometimes fatal, has been reported with use of 5-HT₃ receptor antagonists. Most cases have been observed when 5-HT₃ receptor antagonists are used in conjunction with other serotonergic drugs (eg, selective serotonin reuptake inhibitors [SSRIs], serotonin-norepinephrine reuptake inhibitors [SNRIs], monoamine oxidase inhibitors [MAOIs], mirtazapine, fentanyl, lithium, tramadol, IV methylene blue) or in cases of overdose with other 5-HT₃ receptor antagonists. Most cases of serotonin syndrome have occurred in patients in postanesthesia care units or infusion centers.¹ Patients should be educated to recognize and report signs and symptoms of serotonin syndrome, including 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), seizures, and potential GI symptoms (eg, nausea, vomiting, diarrhea). If serotonin syndrome occurs, immediately discontinue netupitant/palonosetron.¹

A placebo-controlled QTc study showed that doses ranging from netupitant 200 mg/palonosetron 0.5 mg to netupitant 600 mg/palonosetron 1.5 mg did not clinically increase the QTc interval compared with placebo.^{1,20}

Netupitant is classified as Pregnancy Category C; no adequate and well-controlled studies have been performed in pregnant women. Netupitant/palonosetron should only be used in pregnancy if the benefits clearly outweigh the risks. Administration of doses up to 3.7 times the human exposure to pregnant rats did not lead to fetal abnormalities. Administration of doses at

least 0.2 times the human exposure did lead to fetal abnormalities in pregnant rabbits.¹

It is not known if netupitant/palonosetron is excreted in human breast milk. Because many drugs are excreted in human breast milk, caution should be used and a decision to discontinue netupitant/palonosetron or breast-feeding should be made.¹

Safety and efficacy have not been established in patients younger than 18 years.¹

No dosage adjustment is required for patients with mild to moderate hepatic impairment (Child-Pugh score of 5 to 8). Limited data are available concerning the use of netupitant/palonosetron in patients with severe hepatic impairment (Child-Pugh score of 9 or greater); netupitant/palonosetron should be avoided in these patients.¹

No dosage adjustment is required for patients with mild to moderate renal impairment. Although severe renal impairment did not significantly affect the pharmacokinetics of netupitant/palonosetron, safety and efficacy have not been established in this population. Netupitant/palonosetron should be avoided in patients with severe renal impairment or end-stage renal disease requiring hemodialysis.¹

ADVERSE REACTIONS

The most commonly reported adverse reactions in patients receiving netupitant/palonosetron compared with those receiving palonosetron prior to HEC were dyspepsia (4% vs 2%), fatigue (4% vs 2%), constipation (3% vs 1%), and erythema (3% vs 2%). For patients receiving netupitant/palonosetron or palonosetron prior to MEC (eg, anthracyclines, cyclophosphamide-based chemotherapy), the most common adverse events were headache (9% vs 7%), asthenia (8% vs 7%), and fatigue (7% vs 5%).¹

Abnormal laboratory values in patients treated with netupitant/palonosetron or palonosetron were aspartate aminotransferase (AST) greater than 3 times the upper limit of normal (ULN) and/or alanine aminotransferase (ALT) greater than 3 times the ULN with total bilirubin greater than ULN (0.3% vs 0.6%); AST greater than 10 times the ULN and/or ALT greater than 10 times the ULN with total bilirubin greater than the ULN (0% vs 0.2%); and AST greater than 3 times the ULN and/or ALT greater than 3 times the ULN with total bilirubin 2 times the ULN or greater (0.1% vs 0.1%).¹

In a trial for the treatment of overactive bladder, healthy patients undergoing daily dosing of netupitant 200 mg for up to 8 weeks had a higher rate of

somnolence (10% vs 5%), headache (3.3% vs 0%), first-degree atrioventricular block (3.3% vs 1.7%), tachycardia (3.3% vs 0%), and nausea (3.3% vs 0%) compared with the placebo group.²⁵

DRUG INTERACTIONS

Coadministration of netupitant and midazolam (a CYP3A4 substrate) increased midazolam's $C_{\max}$ by 40%, AUC_{inf} by 144%, and mean half-life by 64%. The clearance of midazolam was decreased 52%. The pharmacokinetics of netupitant were not affected by the presence of midazolam.^{1,26} Caution should be used when administering netupitant/palonosetron with benzodiazepines metabolized via CYP3A4 (eg, alprazolam, midazolam, triazolam).¹

Coadministration of netupitant and erythromycin increased erythromycin's $C_{\max}$ by 30%, AUC_{inf} by 30%, and mean half-life by 17%. The clearance of erythromycin was decreased by 44%. The pharmacokinetics of netupitant were not affected by the presence of erythromycin.²⁶

Coadministration of netupitant 300 mg and dexamethasone (20 mg on day 1 followed by 8 mg twice daily on days 2 to 4) increased dexamethasone's AUC_{0-24} by 72% on day 1, AUC_{24-36} by 143% on day 2, AUC_{84-108} by 140%, and $AUC_{84-\text{inf}}$ by 140% compared with dexamethasone alone. The $C_{\max}$ of dexamethasone was increased by 11% on day 1, by 66% on day 2, and by 75% on day 4. The half-life of dexamethasone was increased by 1.9 to 3.2 hours on day 1 and by 2 to 2.4 hours on day 4. The pharmacokinetics of netupitant were not affected by the presence of dexamethasone.^{1,26} A dosage reduction is recommended for dexamethasone.¹

Coadministration of netupitant/palonosetron with chemotherapeutic agents metabolized by CYP3A4 (eg, docetaxel, paclitaxel, etoposide, irinotecan, cyclophosphamide, ifosfamide, imatinib, vinorelbine, vinblastine, vincristine) may increase the systemic exposure of these chemotherapeutic agents. Caution should be used, and patients should be monitored closely for adverse reactions due to chemotherapy.¹ One study reported that coadministration of netupitant/palonosetron and cyclophosphamide did not lead to increased rates of adverse events (neutropenia, alopecia, and leukopenia) over at least 4 cycles of chemotherapy.²⁷

Coadministration of oral contraceptives containing levonorgestrel and ethinyl estradiol with netupitant/palonosetron is unlikely to affect the efficacy of the oral contraceptive.^{1,21}

Coadministration of strong inducers of CYP3A4 (eg, rifampin) may reduce the efficacy of netupitant/palonosetron by reducing the plasma concentrations of netupitant. Avoid coadministration of strong inducers of CYP3A4 and netupitant/palonosetron.^{1,21}

Coadministration of strong inhibitors of CYP3A4 (eg, ketoconazole) may increase the systemic exposure of netupitant. No dosage adjustment is recommended.^{1,21}

Coadministration of serotonergic drugs and netupitant/palonosetron may put patients at risk of serotonin syndrome. Monitor for and educate patients about the signs and symptoms of serotonin syndrome during treatment with netupitant/palonosetron.¹

Coadministration of digoxin and netupitant 450 mg did not significantly affect the pharmacokinetics of digoxin. Administration of netupitant and P-glycoprotein may not require dosage adjustments.²⁸

RECOMMENDED MONITORING

All patients should be monitored for adverse events due to excessive levels of chemotherapeutic agents metabolized by CYP3A4. Additionally, when multiple serotonergic agents are used, patients should be monitored for signs and symptoms of serotonin syndrome.¹

Patients should be both warned of increased sedation due to benzodiazepines metabolized by CYP3A4 and monitored for these effects. The increased effect of benzodiazepines can last for multiple days.¹

DOSING

The recommended dose for patients undergoing HEC is 1 capsule of netupitant 300 mg/palonosetron 0.5 mg orally 1 hour prior to chemotherapy, followed by dexamethasone 12 mg 30 minutes prior to chemotherapy on day 1. Additionally, patients should be administered dexamethasone 8 mg orally once daily on days 2 through 4.¹

For patients undergoing MEC (eg, anthracyclines, cyclophosphamide-based chemotherapy, chemotherapy not considered to be highly emetogenic), the recommended dose is 1 capsule of netupitant 300 mg/palonosetron 0.5 mg orally 1 hour prior to chemotherapy, followed by dexamethasone 12 mg orally 30 minutes prior to chemotherapy on day 1. Administration of dexamethasone on days 2 to 4 is not necessary.¹

Netupitant/palonosetron can be taken without regard to food.¹

Dosing for 5-HT₃ antagonists and NK₁ inhibitors for CINV and postoperative nausea and vomiting (PONV) are summarized in Table 6 and Table 7, respectively.^{1,3,5,6,12-14}

PRODUCT AVAILABILITY

Netupitant/palonosetron was approved by the FDA on October 10, 2014.² It is available as a pack of 1 hard gelatin, white and caramel-colored capsule

Table 6. Dosing for 5-HT₃ antagonists and NK₁ inhibitors in chemotherapy-induced nausea and vomiting^{1,3,5,6,12,13,14}

		Infusion time	Day 1	Days 2 to 3	Day 4
Netupitant/ Palonosetron	Oral capsule (HEC)	N/A ^a	One capsule 1 h prior to chemotherapy + dexamethasone 12 mg PO 30 min prior to chemotherapy	Dexamethasone 8 mg PO once daily	Dexamethasone 8 mg PO once daily
	Oral capsule (MEC)	N/A	One capsule 1 h prior to chemotherapy + dexamethasone 12 mg PO 30 min prior to chemotherapy	—	—
Dolasetron	Oral tablet	N/A	Adults: 100 mg 1 h prior to chemotherapy	—	—
			Pediatric patients 2 to 16 years old: 1.8 mg/kg (maximum, 100 mg) 1 h prior to chemotherapy (may use injection solution as oral dose)	—	—
	Injectable solution	N/A	Contraindicated		
Palonosetron	Injectable solution	Adults: 30 sec	Adults: 0.25 mg 30 min prior to chemotherapy	—	—
		Pediatrics: 15 min	Pediatrics 1 month to younger than 17 years: 20 mcg/kg (maximum, 1.5 mg) 30 min prior to chemotherapy	—	—
Ondansetron	Injectable solution	15 min	Adults and pediatric patients 6 months to 18 years old: Three 0.15 mg/kg doses (maximum, 16 mg/dose) 30 min prior to chemotherapy, 4 h after the first dose, and 8 h after the first dose	—	—
	Oral tablet, ODT, Oral solution, ODF (HEC)	N/A	Adults: 24 mg 30 min prior to chemotherapy	Not studied	
	Oral tablet, ODT, Oral solution, ODF (MEC)	N/A	Adults and pediatric patients 12 years and older: 8 mg 30 min prior to chemotherapy, followed by 8 mg 8 h after the first dose	Adults: 8 mg twice daily	—
			Pediatric patients 4 to 11 years old: 4 mg 30 min prior to chemotherapy, followed by 4 mg 4 and 8 h after the initial dose	Pediatric patients 4 to 11 years old: 4 mg 3 times daily	—

(continued)

Table 6. Dosing for 5-HT₃ antagonists and NK₁ inhibitors in chemotherapy-induced nausea and vomiting^{1,3,5,6,12,13,14} (CONT.)

Granisetron	Injectable solution	30 sec or 5 min	Adults and pediatric patients 2 to 16 years old: 10 mcg/kg 30 min prior to chemotherapy	—	—
	Oral tablet	N/A	Adults: 2 mg 1 h prior to chemotherapy <u>OR</u> 1 mg 1 h prior to chemotherapy followed by 1 mg 12 h after the first dose	No benefit	No benefit
	Oral solution	N/A			
	Transdermal patch	N/A	Adults: One patch at least 24 h and up to 48 h prior to chemotherapy; patch can be left on for up to 7 days		
Aprepitant	Oral tablet (HEC)	N/A	125 mg + dexamethasone 12 mg + 5-HT ₃ antagonist 1 h prior to chemotherapy	80 mg + dexamethasone 8 mg	Dexamethasone 8 mg
	Oral tablet (MEC)	N/A	125 mg + dexamethasone 12 mg + 5-HT ₃ antagonist 1 h prior to chemotherapy	80 mg	None
Fosaprepitant	Injectable solution (HEC, 1-day dosing)	20 to 30 min	150 mg + dexamethasone 12 mg + 5-HT ₃ antagonist 30 min prior to chemotherapy	Dexamethasone 8 mg on day 2; dexamethasone 8 mg twice daily on day 3	Dexamethasone 8 mg twice daily
	Injectable solution (HEC, 3-day dosing)	15 min	115 mg + dexamethasone 12 mg + 5-HT ₃ antagonist 30 min prior to chemotherapy	80 mg PO + dexamethasone 8 mg	Dexamethasone 8 mg
	Injectable solution (MEC)	15 minutes	115 mg + dexamethasone 12 mg + 5-HT ₃ antagonist 30 min prior to chemotherapy	80 mg PO	—

Note: h = hours; HEC = highly emetogenic chemotherapy; MEC = moderately emetogenic chemotherapy; min = minutes; N/A = not applicable; ODF = orally disintegrating film; ODT = orally disintegrating tablet; PO = orally; sec = seconds.

containing 3 netupitant 100 mg tablets and 1 palonosetron 0.5 mg gelatin capsule.¹

Netupitant/palonosetron should be stored between 68°F and 77°F (20°C and 25°C), with excursions permitted between 59°F and 86°F (15°C and 30°C).¹

The availability of 5-HT₃ antagonists and NK₁ inhibitors is summarized in Table 8.^{1,3-14,29}

DRUG SAFETY/RISK EVALUATION AND MITIGATION STRATEGY (REMS)

No REMS is required for netupitant/palonosetron.²

CONCLUSION

Netupitant/palonosetron is the first approved combination product containing a 5-HT₃ receptor

antagonist and an NK₁ receptor antagonist. ESMO/MASCC guidelines recommend combination therapy for HEC regimens. The efficacy studies used a single dose with an extension or a 6-cycle dose. One study included aprepitant with ondansetron, but the study was not designed to compare netupitant/palonosetron with this arm and did not perform statistical analysis between the groups. While palonosetron was previously approved and has been used clinically in a large population, experience with netupitant is limited. Netupitant monotherapy was studied for a different indication at a dose of 200 mg daily for 8 weeks and showed an adverse effect profile similar to those of short-term studies. Netupitant/palonosetron has not been studied for the treatment of nausea.

Table 7. Dosing for 5-HT₃ antagonists and NK₁ inhibitors in postoperative nausea and vomiting^{1,3,5,6,12-14}

		Infusion time	Adults	Pediatric patients
Netupitant/ Palonosetron	Oral capsule	N/A	Not approved	
Dolasetron	Injectable solution	30 sec or 15 min	12.5 mg IV 15 min before cessation of anesthesia OR 12.5 mg IV as soon as nausea or vomiting is present	2 to 16 years old: 0.35 mg/kg (maximum, 12.5 mg) IV 15 minutes before cessation of anesthesia OR as soon as nausea or vomiting is present
Palonosetron	Injectable solution	10 sec	0.075 mg IV immediately prior to induction of anesthesia	Not approved
Ondansetron	Injectable solution	Preferably 2 to 5 min; 30 sec is an option	4 mg IV immediately prior to induction of anesthesia or postoperatively	1 month to 12 years old: • Weight < 40 kg: 0.1 mg/kg IV • Weight 40 kg or greater: 4 mg IV immediately prior to induction of anesthesia or postoperatively
	Oral tablet, ODT, Oral solution, ODF	N/A	16 mg orally 1 h prior to induction of anesthesia	Not approved
Aprepitant	Oral tablet	N/A	40 mg within 3 h prior to induction of anesthesia	Not approved

Note: h = hours; IV = intravenous; min = minutes; NA = not applicable; ODF = orally disintegrating film; sec = seconds.

Table 8. Availability for 5-HT₃ antagonists and NK₁ inhibitors^{1,3-14,29}

Generic name	Dosage form	Proprietary name	Strengths	Pack size	Generic availability
Netupitant/ Palonosetron	Oral capsule	<i>Akynzeo</i>	300 mg/0.5 mg	1 capsule	No
Dolasetron	Injectable solution	<i>Anzemet</i>	20 mg/mL	0.625 mL (6 vials), 5 mL (1 single-dose vial), 25 mL (1 multidose vial)	Yes
			50 mg	5-count bottle, 10-count unit-dose pack	Yes
	Oral tablet	<i>Anzemet</i>	100 mg	5-count bottle, 5-count blister pack, 10-count unit-dose pack	Yes
Palonosetron	Injectable solution	<i>Aloxi</i>	0.05 mg/mL	1.5 mL (5 vials), 5 mL (1 vial)	No
Ondansetron	Injectable solution	<i>Zofran</i>	2 mg/mL	2 mL (24 prefilled syringes, 25 single-dose vials), 20 mL (multidose vial)	Yes
	Oral tablet	<i>Zofran</i>	4 mg, 8 mg	Pack of 3 tablets, bottle of 30 tablets	Yes
	ODT	<i>Zofran</i>	4 mg, 8 mg	Pack of 30 tablets	Yes
	Oral solution	<i>Zofran</i>	4 mg/5 mL	50 mL bottle	Yes
	ODF	<i>Zuplenz</i>	4 mg	Box of 10	No
			8 mg	Box of 10	No

(continued)

Table 8. Availability for 5-HT₃ antagonists and NK₁ inhibitors^{1,3-14,29} (CONT.)

Granisetron	Injectable solution	<i>Kytril</i>	1 mg/mL	1 mL (single-dose vial, pack of 1), 4 mL (multidose vial, pack of 1)	Yes
		<i>Kytril</i>	0.1 mg/mL	1 mL (single-dose vial, pack of 10)	Yes
	Oral tablet	<i>Kytril</i>	1 mg	Pack of 2 tablets, pack of 20 tablets	Yes
	Oral solution	<i>Granisol</i>	2 mg/10 mL	30 mL bottle	No (discontinued)
	Transdermal patch	<i>Sancuso</i>	3.1 mg per 24 hours	Single patch	No
Aprepitant	Oral tablet	<i>Emend</i>	40 mg	Pack of 1 tablet, pack of 5 tablets	No
			80 mg	Pack of 2 tablets, pack of 6 tablets	No
			125 mg	Pack of 6 tablets, tripack with one 125 mg tablet and two 80 mg tablets	No
Fosaprepitant	Injectable solution	<i>Emend</i>	115 mg	1 single-dose vial	No
			150 mg	1 single-dose vial	No

Note: ODF = orally disintegrating film; ODT = orally disintegrating tablet.

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Continuing Education Case Study Quiz

Goal—The goal of this activity is to educate pharmacists about the use of netupitant/palonosetron for the treatment of patients with chemotherapy-induced nausea and vomiting.

Objectives—At the completion of this activity, the reader will be able to:

1. Describe the pharmacology and pharmacokinetics of netupitant/palonosetron.
2. Discuss the risks associated with the use of netupitant/palonosetron.
3. Discuss the potential benefit of netupitant/palonosetron for an individual patient.
4. Apply the information on the use of netupitant/palonosetron to a case study.

Key Words—antiemetics, chemotherapy-induced nausea and vomiting, netupitant/palonosetron, new drugs

This CE activity is jointly provided by ProCE, Inc. and *Hospital Pharmacy*. ProCE, Inc. is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. ACPE Universal Activity Number 0221-9999-15-043-H01-P has been assigned to this knowledge-based home-study CE activity (initial release date 04-01-2015). This CE activity is approved for 1.5 contact hours (0.15 CEUs) in states that recognize ACPE providers. This CE activity is provided at no cost to participants. Completion of the evaluation and the post-test with a score of 70% or higher are required to receive CE credit. No partial credit will be given.

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1. The US Food and Drug Administration (FDA)–approved indication for netupitant/palonosetron is for the prevention of:
 - A. Nausea and vomiting after irradiation.
 - B. Acute and delayed chemotherapy-induced nausea and vomiting.
 - C. Hyperemesis gravidarum.
 - D. Postoperative nausea and vomiting.
2. Netupitant/palonosetron produces its antiemetic effects by inhibition of:
 - A. Dopamine receptors.
 - B. Neurokinin-1 receptors only.
 - C. 5-HT₃ receptors only.
 - D. Both neurokinin-1 receptors and 5-HT₃ receptors.

3. In which of the following dosage form is netupitant/palonosetron available?
 - A. Capsules
 - B. Tablets
 - C. Orally dissolving tablets
 - D. Injectable
4. Which of the following is a contraindication to the use of netupitant/palonosetron?
 - A. There are no contraindications to therapy with netupitant/palonosetron.
 - B. Concomitant apomorphine
 - C. Administration with pimozide
 - D. History of serotonin syndrome
5. Netupitant/palonosetron is in which Pregnancy Category?
 - A. A
 - B. B
 - C. C
 - D. X

Case History

K.N. is a 52-year-old female patient with controlled hypertension, hyperlipidemia, depression, and newly diagnosed HER2-negative breast cancer. Her current medications include daily lisinopril, simvastatin, fluoxetine, and as-needed lorazepam. Her physician plans to begin chemotherapy with cyclophosphamide and doxorubicin. Her renal and hepatic function are both normal. Prior to chemotherapy, the following laboratory results were obtained: white blood cell count 37, red blood cell count 4.2, hemoglobin 13.8, hematocrit 38.4%, and platelets 300. Her physician thinks she may benefit from netupitant/palonosetron prior to chemotherapy.

6. K.N. should receive which of the following medications adjunctively with netupitant/palonosetron?
 - A. Metoclopramide
 - B. Prochlorperazine
 - C. Dexamethasone
 - D. Lorazepam
7. What is the recommended dose of netupitant/palonosetron for K.N.?
 - A. 8 mg/ 8 mg
 - B. 24 mg/0.25 mg
 - C. 125 mg/12 mg
 - D. 300 mg/0.5 mg
8. K.N. should receive the netupitant/palonosetron dose:
 - A. 1 hour prior to chemotherapy.
 - B. 30 minutes prior to chemotherapy.
 - C. 1 day before and repeated 30 minutes prior to chemotherapy.
 - D. Concomitantly at the time of chemotherapy administration.
9. What is the total netupitant/palonosetron and dexamethasone dosing duration for K.N.?
 - A. 1 day for netupitant/palonosetron and 2 days for dexamethasone
 - B. 1 day for netupitant/palonosetron and 4 days for dexamethasone
 - C. 2 days for netupitant/palonosetron and 2 days for dexamethasone
 - D. 3 days for netupitant/palonosetron and 4 days for dexamethasone
10. Which of K.N.'s medications may interact with netupitant/palonosetron due to an enzyme-mediated pathway?
 - A. Fluoxetine
 - B. Lisinopril
 - C. Cyclophosphamide
 - D. None of the above
11. Which of the K.N.'s medications may interact with netupitant/palonosetron due to a synergistic mechanism?
 - A. Fluoxetine
 - B. Lisinopril
 - C. Simvastatin
 - D. None of the above
12. What baseline and periodic monitoring would you recommend for K.N.'s netupitant/palonosetron therapy?
 - A. Blood pressure
 - B. Cholesterol panel
 - C. Sedation
 - D. Nausea and vomiting
13. The most common side effects associated with netupitant/palonosetron prior to chemotherapy include:
 - A. Nausea, headache, and diarrhea.
 - B. Dyspepsia, fatigue, and constipation.
 - C. Headache, nausea, and constipation.
 - D. Dyspepsia, abnormal liver function tests, and fatigue

14. Netupitant/palonosetron is supplied in a package containing:
- A. 1 capsule.
 - B. 4 capsules.
 - C. 30 capsules.
 - D. 90 capsules.
15. K.N. is taking the recommended dose of netupitant/palonosetron and has been experiencing severe constipation. Her physician wants

to reduce her dose and has asked you for the recommended dose reduction for adverse events. Which of the following is recommended?

- A. Reduce the dose of dexamethasone.
- B. Open the capsule and take 200 mg netupitant (2 tablets) and 0.5 mg palonosetron.
- C. Open the capsule and take 100 mg netupitant (1 tablet) and 0.5 mg palonosetron.
- D. No dosage reductions are recommended; she may need to change therapy. ■