Drug–drug interaction profile of components of a fixed combination of netupitant and palonosetron: Review of clinical data

James J Natale1, Tulla Spinelli2, Selma Calcagnile2, Corinna Lanzarotti2, Giorgia Rossi2, David Cox3 and Kimia Kashef4

Abstract
Neurokinin-1 (NK1) receptor antagonists (RAs) are commonly coadministered with serotonin (5-HT3) RAs (e.g. palonosetron (PALO)) to prevent chemotherapy-induced nausea/vomiting. Netupitant/palonosetron (NEPA), an oral fixed combination of netupitant (NETU)—a new NK1 RA—and PALO, is currently under development. In vitro data suggest that NETU inhibits CYP3A4 and is a substrate for and weak inhibitor of P-glycoprotein (P-gp). This review evaluates potential drug–drug interactions between NETU or NEPA and CYP3A4 substrates/inducers/inhibitors or P-gp substrates in healthy subjects. Pharmacokinetic (PK) parameters were evaluated for each drug when NETU was coadministered with PALO (single doses) and when single doses of NETU or NEPA were coadministered with CYP3A4 substrates (erythromycin (ERY), midazolam (MID), dexamethasone (DEX), or oral contraceptives), inhibitors (ketoconazole (KETO)), or inducers (rifampicin (RIF)), or a P-gp substrate (digoxin (DIG)). Results showed no relevant PK interactions between NETU and PALO. Coadministration of NETU increased MID and ERY exposure and significantly increased DEX exposure in a dose-dependent manner; NETU exposure was unaffected. NEPA coadministration had no clinically significant effect on oral contraception, although levonorgestrel exposure increased. NETU exposure increased after coadministration of KETO and decreased after coadministration with RIF; PALO exposure was unaffected. NETU coadministration did not influence DIG exposure. In conclusion, there were no clinically relevant interactions between NETU and PALO, or NEPA and oral contraceptives (based on levonorgestrel and ethinylestradiol exposure). Coadministration of NETU or NEPA with CYP3A4 inducers/inhibitors/substrates should be done with caution. Dose reduction is recommended for DEX. Dose adjustments are not needed for NETU coadministration with P-gp substrates.

Keywords
Netupitant, palonosetron, NK1 receptor antagonist, 5-HT3 receptor antagonist, drug interactions

Introduction
Neurokinin-1 (NK1) receptor antagonists (RAs) and serotonin (5-HT3) RAs are two classes of agents recommended for prevention of chemotherapy-induced nausea/vomiting (CINV).1–3 CINV is thought to arise via multiple pathways that are activated by various neurotransmitters, most notably serotonin (5-HT) and substance P, among others.4 The 5-HT3 RAs (ondansetron, dolasetron, granisetron, palonosetron (PALO)) modulate emetic pathways via inhibition of 5-HT3 receptors.
receptors located in both the gastrointestinal tract and the central nervous system.\textsuperscript{3,5} NK\textsubscript{1} RAs (e.g. aprepitant and fosaprepitant) prevent binding of substance P at NK\textsubscript{1} receptors, which are located in the gut, area postrema, and nucleus tractus solitarius (areas involved in the emetic reflex).\textsuperscript{5} Because their mechanisms of action target different neurotransmitter pathways involved in nausea and vomiting, combination therapy with a 5-HT\textsubscript{3} RA and NK\textsubscript{1} RA represents a rational therapeutic strategy.\textsuperscript{5} Indeed, several studies have demonstrated the efficacy of such combinations,\textsuperscript{4} and several guidelines recommend this combination (plus a steroid) for managing CINV associated with highly emetogenic chemotherapy regimens.\textsuperscript{1-3}

Netupitant/palonosetron (NEPA) is an oral fixed combination of netupitant (NETU, 300 mg) and PALO (0.5 mg) recently approved for prevention of acute and delayed CINV. NETU is a novel, highly selective NK\textsubscript{1} RA.\textsuperscript{7} PALO is a pharmacologically distinct 5-HT\textsubscript{3} RA in that it has a different pharmacokinetic (PK) profile and molecular binding profile,\textsuperscript{8} triggers receptor internalization,\textsuperscript{9} demonstrates prolonged inhibition of 5-HT\textsubscript{3} receptor function,\textsuperscript{8,9} and inhibits 5-HT\textsubscript{3}-NK\textsubscript{1} crosstalk.\textsuperscript{10} These characteristics may be responsible for its prolonged duration of action and greater efficacy in preventing delayed CINV (24–120 h after chemotherapy) versus single doses of other 5-HT\textsubscript{3} RAs.\textsuperscript{11,12} A recent in vitro study demonstrated a synergistic effect of NETU and PALO on inhibition of substance P-mediated responses,\textsuperscript{13} and both NETU and PALO triggered NK\textsubscript{1} receptor internalization.\textsuperscript{14} Administration of these two agents as a single oral dose may provide a convenient and noninvasive means of administering guideline-based\textsuperscript{1,5} antiemetic prophylaxis.

Reported results from clinical trials to date have demonstrated the efficacy of NEPA in preventing CINV associated with highly and moderately emetogenic chemotherapy.\textsuperscript{15-18} In a Phase 2 study, patients receiving NEPA had higher rates of complete response (CR; no emesis, no rescue medication) and secondary endpoints (no emesis, no significant nausea, and complete protection (CR + no significant nausea)) in the overall phase compared with patients who received PALO alone.\textsuperscript{17} In one Phase 3 study, patients receiving NEPA had higher CR rates in the delayed, acute, and overall phases than those receiving PALO alone, as well as higher rates of no emesis and no significant nausea during the delayed and overall phases.\textsuperscript{15} Efficacy of NEPA over multiple cycles of chemotherapy was demonstrated in two Phase 3 studies.\textsuperscript{16,18} In all studies, NEPA was well tolerated, with a safety profile similar to that of controls (e.g. PALO alone, PALO plus aprepitant, or aprepitant plus ondansetron).\textsuperscript{15-18}

The drug–drug interaction (DDI) profile of any potentially new antiemetic is an important consideration for its place in therapy. As outlined already, combination therapy with multiple antiemetic agents is necessary to target the many pathways that are stimulated after chemotherapy administration. In addition, often these patients are on many other chronic medications as well as the chemotherapy they are receiving so the possibility of DDIs generally is heightened. PALO is primarily metabolized by cytochrome P450 (CYP) enzyme 2D6 (CYP2D6), and to a lesser extent, by CYP3A4 and CYP1A2.\textsuperscript{19} In vitro studies demonstrated that PALO neither inhibits nor induces activity of CYP enzymes.\textsuperscript{20} NETU is primarily metabolized by CYP3A4.\textsuperscript{21} In vitro data suggest that NETU inhibits CYP3A4\textsuperscript{22} and is a substrate for and a weak inhibitor of P-glycoprotein (P-gp)\textsuperscript{23} but does not inhibit CYP1A2, 2C9, 2C19, or 2D6.\textsuperscript{22}

In this article, we review a series of clinical studies that were conducted to evaluate potential DDIs with NETU or NEPA.

**Combination 5-HT\textsubscript{3} and NK\textsubscript{1} RA**

**NETU and PALO**

Because NETU and PALO will be used as an oral fixed combination in clinical practice, it is important to determine whether coadministration affects the PK profile of either drug. A randomized, open-label, single-dose, three-period crossover study assessed the effects of PALO on the PKs of NETU and the effects of NETU on the PKs of PALO.\textsuperscript{21} Healthy subjects (nine men and nine women aged 18–43) received single doses of NETU (450 mg PO) alone, PALO (0.75 mg PO) alone, and NETU and PALO combined, with a minimum 14-day washout before the following period. The primary PK parameters of interest included maximum serum concentration (C\textsubscript{max}), area under the curve (AUC) from administration to the last sampling point (AUC\textsubscript{last}) and extrapolated to infinity (AUC\textsubscript{inf}). Log-transformed values were analyzed using analysis of covariance. Safety assessments included adverse events (AEs), physical exam, vital signs, electrocardiogram (ECG), and laboratory tests.

C\textsubscript{max}, AUC\textsubscript{last}, and AUC\textsubscript{inf} for PALO were similar after administration alone and in combination with NETU. Exposure to PALO was slightly higher after coadministration with NETU, but the difference appeared to be of no clinical relevance (i.e. 90% confidence intervals (CIs) of the geometric mean ratios of PK parameters associated with the drugs given alone or in combination fell within the classical bioequivalence limits of 80%–125%) (Table 1). C\textsubscript{max}, AUC\textsubscript{last}, and AUC\textsubscript{inf} for NETU were similar after administration alone and in combination with PALO. The most common AEs were headache (61%), nasopharyngitis
(39%), nausea (28%), somnolence (28%), constipation (17%), abdominal pain (17%), abdominal pain upper (11%), and dizziness (11%). All AEs were mild or moderate in intensity; overall, the study treatments were well tolerated by subjects.

This study demonstrated that there were no clinically (nor statistically) relevant PK interactions between NETU and PALO with single doses of 450 mg and 0.75 mg, respectively.21 Of note, these doses are higher than those used in the NEPA combination product.

**NETU or NEPA and CYP3A4 substrates**

**NETU and midazolam or erythromycin**

As noted above, in vitro data suggest that NETU moderately inhibits CYP3A4.22 Midazolam (MID) and erythromycin (ERY) are representative CYP3A4 substrates24 and can be used as probes to determine whether and the extent to which NETU affects CYP3A4 activity in healthy volunteers. The impact of NETU on the PKs of MID and ERY, and the effect of MID or ERY on the PKs of NETU, were assessed in a single-dose, three-period crossover study.24 Subjects (20 healthy men, age range 20–32) were randomly assigned to one of four treatment sequences with oral MID (7.5 mg) or ERY (500 mg) alone alternating with oral NETU (300 mg) alone, followed by a combination of MID or ERY with NETU (minimum three-week washout between periods). Endpoints included PK parameters for MID, ERY, and NETU, including Cmax, time to maximum serum concentration (tmax), elimination half-life (t1/2), AUClast, and AUCinf. Safety assessments included routine laboratory tests, physical exams, vital signs, 12-lead ECGs, and AEs.

Exposure to MID was significantly increased when coadministered with NETU (Table 2); mean Cmax increased by 40%, and mean AUC was 144% higher (Figure 1). Exposure to ERY was significantly increased when coadministered with NETU (Table 2); mean Cmax and AUC were both 30% higher. The PKs of NETU were not significantly altered by coadministration with MID or ERY. Treatments were well tolerated: the majority of AEs were mild, and the most frequent were fatigue (10%), headache (8.3%), lethargy (6.7%), and nausea (5%); no serious AEs or deaths occurred during the study. No clinically significant changes in laboratory parameters, vital signs, or ECGs were observed.

This study demonstrated that coadministration of single doses of NETU, at doses intended for CINV prophylaxis, altered the PKs of MID and ERY via moderate inhibition of CYP3A4 metabolism. Exposure of NETU following a single dose of 300 mg was unaffected by coadministration with either of the CYP3A4 substrates, ERY or MID, at therapeutic doses.24

**NETU and dexamethasone**

Dexamethasone (DEX) is a substrate of CYP3A4.24 Considering the likelihood that NETU or NEPA will be coadministered with DEX in clinical practice, this potential DDI is of particular clinical interest. The effects of NETU on the PKs of DEX (primary objective) were assessed in 25 healthy adults (14 men and 11 women aged 18–42).24 Secondary objectives of the study were to assess the safety and tolerability of NETU with concomitant administration of DEX and the effects of DEX on the PKs of NETU. In a randomized, open-label, three-period crossover study,
subjects received oral DEX (20 mg on Day 1 followed by 8 mg twice daily (every 12 h) on Days 2–4) alone or in combination with oral NETU (100, 300, and 450 mg) administered on Day 1 only, with a minimum 14-day washout between periods. Endpoints included, for DEX: C\text{max} (after the 20-mg dose, first 8-mg dose, and last 8-mg dose), AUC for time intervals 0–24, 24–36, and 84–108 h post-first DEX dose, C\text{min} (DEX: after each 8-mg dose), t\text{1/2} (after the 20-mg dose and last 8-mg dose), and t\text{max} on Days 1, 2, and 4; for NETU: C\text{max}, AUC\text{0–24}, AUC\text{last}, and AUC\text{inf}. Safety assessments included 12-lead ECG, blood pressure, and pulse rate; AEs were also reported.

NETU increased exposure to DEX in a dose-dependent manner (Figure 2, Table 3). On Day 1, DEX mean AUC\text{0–24} increased by 48%, 72%, and 75% with coadministration of 100, 300, and 450 mg NETU, respectively, while C\text{max} was only slightly affected (9%–20% increases). On Day 4, DEX mean AUC\text{84–108} increased by 75%, 140%, and 170% with coadministration of 100, 300, and 450 mg NETU, respectively. On Days 2 and 4, DEX C\text{max} increased by 49%–79%. DEX C\text{min} on Days 2–4 was increased approximately 180%, 330%, and 360% with coadministration of 100, 300, and 450 mg NETU, respectively. The PK profile of NETU was not significantly altered in the presence of

**Table 2.** Effects of NETU on ERY and MID pharmacokinetics.

|                      | MID alone (% CV) | MID + NETU (% CV) | Mean ratio (90% CI) |
|----------------------|------------------|-------------------|---------------------|
| C\text{max} (ng/mL) | 29.1 (47.7)      | 40.6 (49.8)       | 136 (116–159)       |
| AUC\text{inf} (ng·h/mL) | 122 (38.6) | 298 (54.4)       | 226 (189–270)       |
| t\text{1/2} (h)    | 3.75 (37.2)      | 6.16 (23.3)       |                     |
| CL/F (L/h)         | 72.6 (51.3)      | 34.6 (62.1)       |                     |

**Figure 1.** Effect of NETU on MID and ERY plasma concentrations.24

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ERY: erythromycin; MID: midazolam; NETU: netupitant.

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DEX; PK parameters for NETU were comparable to results obtained in previous studies in which the same doses of NETU were administered alone.

Treatments were well tolerated: the most common AEs were acne (56%), headache (56%), nausea (40%), flushing (36%), nasopharyngitis (32%), fatigue (24%), and insomnia (24%). No deaths or serious AEs occurred during the study. No clinically significant changes in laboratory parameters, vital signs, or ECGs were noted.

This study demonstrated that coadministration of single doses of NETU significantly increased exposure to DEX in a dose-dependent manner, and the findings suggest that oral doses of DEX should be reduced by ~50% when given in combination with NETU. Therapeutic doses of DEX when administered with

Table 3. Effects of NETU on DEX pharmacokinetics.24

|                  | DEX + NETU100 vs. DEX alone | DEX + NETU300 vs. DEX alone | DEX + NETU450 vs. DEX alone |
|------------------|-----------------------------|-----------------------------|-----------------------------|
|                  | Point estimate (%) 90% CI   | Point estimate (%) 90% CI   | Point estimate (%) 90% CI   |
| AUC (µg·h/L)     |                             |                             |                             |
| AUC0–24          | 148.01 135.41–161.77        | 171.62 156.71–187.95        | 175.35 160.61–191.45        |
| AUC24–36         | 208.7 187.32–232.52         | 243.02 217.67–271.33        | 258.32 232.17–287.42        |
| AUC94–108        | 174.33 161.8–187.83         | 238.17 220.67–257.06        | 267.32 248.34–287.76        |
| Cmax (µg/L)      |                             |                             |                             |
| Cmax0–24         | 109.45 101–118.62           | 111.01 102.26–120.51        | 119.95 110.8–129.87         |
| Cmax24–36        | 169.95 153.79–187.82        | 166.33 150.25–184.13        | 173.37 157.08–191.36        |
| Cmax94–108       | 148.98 132.74–167.21        | 174.9 155.46–196.78         | 178.55 159.31–200.11        |
| Cmin (µg/L)      |                             |                             |                             |
| Cmin24–36        | 325.49 276.08–383.73        | 487.1 411.82–576.13         | 486.95 413.88–572.93        |
| Cmin36–48        | 292.04 252.41–337.88        | 416.89 359.25–483.77        | 462.25 400.25–533.85        |
| Cmin48–60        | 303.06 259.37–354.11        | 512.66 437.32–600.98        | 485.41 416.24–566.09        |
| Cmin60–72        | 250.64 216.84–289.7         | 388.73 335.3–450.69         | 389.85 337.89–449.8         |
| Cmin72–84        | 215.42 152.85–303.6         | 348.02 245.54–493.29        | 463.42 330.22–650.36        |

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AUC: area under the curve; CI: confidence interval; Cmax: maximum serum concentration; Cmin: minimum serum concentration; DEX: dexamethasone; NETU: netupitant.

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Figure 2. Pharmacokinetic effects of NETU on DEX concentrations.24
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NETU: netupitant; DEX: dexamethasone.
NETU appear to have no effect on the exposure of NETU.  

**NEPA and ethinylestradiol or levonorgestrel**

DDIs that reduce the efficacy of oral contraceptives are also of interest as a potential scenario that may need to be managed in clinical practice. The effect of NEPA on the PKs of ethinylestradiol (EE) and levonorgestrel (LEVO) was evaluated in a randomized, open-label, single-dose, two-period crossover study. Subjects (24 healthy women aged 19–40) received single doses of EE/LEVO (60 μg/300 μg PO) alone and in combination with NEPA (300 mg/0.5 mg PO) with a minimum 28-day washout between periods. Endpoints included PK parameters for EE and LEVO: Cmax, AUClast, and AUCinf. Safety assessments included AEs, vital signs, physical exam, ECG, and clinical laboratory tests.

PK parameters for EE and LEVO are summarized in Table 4. NEPA did not significantly affect exposure to EE, with AUClast and AUCinf increased by 16% and 12%, respectively. These changes were not clinically relevant, as the 90% CIs were within the 80%–125% bioequivalence range. Cmax for LEVO was not altered following coadministration with NEPA. However, the extent of LEVO exposure was significantly higher after NEPA coadministration. AUClast and AUCinf for LEVO were 46% and 40% higher, respectively, and the 90% CIs were outside the 80%–125% bioequivalence range. The most common AEs were headache (58%), nausea (29%), constipation (25%), fatigue (21%), dizziness (13%), diarrhea (8%), vomiting (8%), and metrorrhagia (8%). All AEs were mild to moderate in intensity; no subjects experienced serious clinical, laboratory, or other AEs.

These data demonstrate that coadministration of single doses of NEPA did not significantly affect exposure to EE. Although NEPA coadministration increased exposure to LEVO by approximately 40%, the observed change is not considered clinically relevant. Therefore, no dose adjustment or precaution is necessary.

**NEPA and CYP3A4 inhibitors and inducers**

**NEPA and ketoconazole or rifampicin**

As a substrate of CYP3A4, NETU is also susceptible to DDIs with CYP3A4 inhibitors or inducers that may affect its PKs. One study evaluated coadministration of NEPA with a strong CYP3A4 inhibitor (ketoconazole (KETO)) or a strong CYP3A4 inducer (rifampicin (RIF)). A two-group, two-way crossover study was conducted to assess the effect of KETO and RIF on the PKs of NEPA in healthy subjects. Subjects (21 men and 15 women, age range 32–55) received a single oral dose of NEPA on Day 1, alone or in combination with KETO (400 mg PO QD, from Days -2 to 10) or RIF (600 mg PO QD, from Days -7 to 10), with a minimum 28-day washout period between NEPA doses (half the subjects received KETO and half received RIF). Endpoints included PK parameters for NETU and PALO including Cmax, AUClast, and AUC0-infinity; safety assessments included AEs, laboratory parameters, vital signs, and ECG.

NETU exposure was significantly increased after administration of NEPA in combination with KETO, with an increase of 80% for AUClast, 140% for AUC0-infinity, and 25% for Cmax (Table 5). PALO

**Table 4. Effect of NEPA on EE/LEVO pharmacokinetics.**

| Parameter | EE/LEVO Mean (SD) | EE/LEVO + NEPA Mean (SD) | Mean ratio (90% CI) |
|-----------|------------------|-------------------------|---------------------|
| Cmax (pg/mL) | 115.6 (30.9) | 120.6 (28.3) | 105.1 (98.3–112.3) |
| AUClast (pg·h/mL) | 928.3 (383.2) | 1071 (397) | 116.1 (106.2–126.8) |
| AUC0-infinity (pg·h/mL) | 1091 (400.9) | 1224 (428.7) | 112.1 (102.8–122.2) |
| Cmax (ng/mL) | 8.23 (2.79) | 8.11 (2.93) | 98.1 (92.5–103.9) |
| AUClast (ng·h/mL) | 60.0 (37.0) | 87.4 (54.1) | 146.2 (129.4–165.2) |
| AUC0-infinity (ng·h/mL) | 80.4 (42.4) | 113.1 (63.5) | 139.6 (123.6–157.6) |

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AUC: area under the curve; CI: confidence interval; Cmax: maximum serum concentration; EE: ethinylestradiol; LEVO: levonorgestrel; NEPA: netupitant/palonosetron; SD: standard deviation.
exposure was not significantly affected by KETO coadministration. NETU exposure was significantly decreased after administration of NEPA in combination with RIF, with a decrease of 82% for AUC_{last}, 83% for AUC_{0–inf}, and 62% for C_{max} (Table 6). AUC_{last} and AUC_{0–inf} for PALO were slightly decreased (19%) by coadministration with RIF; these changes were not considered clinically relevant, and the 90% CIs were within the predefined 80%–125% equivalence range. The most common AEs were fatigue (57%), headache (40%), nasopharyngitis (20%), diarrhea (11%), abdominal pain (9%), constipation (9%), nausea (9%), and rhinitis (9%). Most of the observed AEs were of mild intensity (101 of 107 treatment-emergent AEs) and assessed as possibly related to the treatment (92 of 107 treatment-emergent AEs). No events of severe intensity were reported. No subjects experienced serious clinical, laboratory, or other AEs.

This study demonstrated that NETU exposure was increased after administration of NEPA in combination with KETO and decreased after administration of NEPA in combination with RIF, while the PKs of PALO were not significantly affected by either KETO or RIF. 21

**P-gp substrates**

**NETU and digoxin**

The drug transporter P-gp is another potential source of DDIs, and there is some overlap with CYP3A4 in terms of substrates, inhibitors, and inducers. 25
Digoxin (DIG), a substrate for P-gp, is often used as a probe to assess the effects of drugs on P-gp function. A one-way, fixed-sequence study assessed the effects of NETU on the PKs of DIG at steady state during the first 24-h post-NETU dose in healthy volunteers. Secondary objectives of the study were to evaluate the PKs of NETU given concomitantly with DIG and the safety and tolerability of NETU with concomitant administration of DIG. Sixteen subjects (eight men and eight women) received a DIG loading dose of 3 mg (0.5 mg PO Q6h) on Day 1, followed by DIG (0.25 mg PO) daily on Days 2–12, with concomitant NETU (450 mg PO) on Day 8. Endpoints included PK parameters for DIG: AUC0–24,ss (ss = at steady state), Cmax,ss, Cmin,ss; safety assessments included AEs, vital signs, and laboratory parameters.

DIG concentrations and exposure at steady state were not altered following concomitant NETU administration (Figure 3). Mean AUC0–24,ss values were 11.37 µg·h/mL for NETU plus DIG and 10.96 µg·h/mL for DIG alone; mean Cmin,ss values were 0.314 µg/mL and 0.322 µg/mL, respectively. The 90% CIs for AUC0–24,ss and for Cmin,ss were within the 80%–125% equivalence limits (95.86%–113.11% and 88.84%–105.14%, respectively). The CIs were slightly outside the upper bound of 125% for Cmax,ss (90.30%–131.49%), but this was considered not clinically relevant. Excretion of DIG in urine was 55% without NETU compared with 57% after NETU coadministration. There were no gender differences observed in extent of exposure to DIG. The PKs of NETU were comparable to previous study results. Study treatment overall was well tolerated; no safety-related influence of DIG and NETU was observed on safety laboratory, vital sign, and ECG parameters. No clinically meaningful influence on QTc was observed.

No influence on DIG exposure after coadministration of a single dose of NETU was observed. Based on these data, dose adjustment for P-gp substrates is not required when administered concomitantly with NETU.

### Summary and discussion

Table 7 summarizes the overall findings from the studies discussed above. No clinically relevant interactions were observed between NETU and PALO or NEPA and oral contraceptives. However, coadministration
of NETU or NEPA with CYP3A4 inducers, inhibitors, and substrates should be done with caution, as dose adjustments may be needed;21,24 dose reduction is recommended for DEX when coadministered with NEPA.24 Dose adjustments are not needed for NETU coadministration with P-gp substrates.23

The findings observed in most of these studies are similar to what has been reported in DDI studies involving aprepitant. For example, studies with PALO27 and DIG20 administered with aprepitant showed no significant effects of aprepitant on either drug, and dose adjustments are not required. Like NETU, aprepitant is a CYP3A4 substrate and is a moderate inhibitor of CYP3A4;28 the AUC and half-life of aprepitant were increased following coadministration with KETO and decreased following coadministration with RIF.29 Studies with MID showed moderate and dose-dependent inhibition of CYP3A4 by aprepitant.29–31 Likewise, the addition of aprepitant to a standard regimen of ondansetron plus oral DEX significantly increased the AU(C)0-24 of DEX,32 and dose adjustments for oral DEX (50% reduction) are recommended.31 Aprepitant has also been shown to exert an inductive effect on CYP3A4; in a study using intravenous MID as a probe, administration of a standard three-day regimen of aprepitant was associated with weak CYP3A4 inhibition on Day 4 and weak induction on Day 8, with no effect on Day 15.33 NETU and its metabolites have not shown any inductive effects on CYP3A4.34

There are some differences in the DDI profile of aprepitant compared with what is currently known about NETU. For example, while NEPA did not demonstrate a clinically relevant interaction with oral contraceptives, aprepitant may reduce the efficacy of hormonal contraception and a backup method of contraception is recommended.29,31 Aprepitant is also a mild inducer of CYP2C9, which can affect the metabolism of tolbutamide.33 NETU, however, has not been shown to induce CYP2C9.34

Several studies have evaluated the effects of aprepitant on the PKs of chemotherapeutic agents; aprepitant did not have a clinically significant effect on the PKs of cyclophosphamide, docetaxel, and vinorelbine, and dose adjustments are not required.31 Systemic exposure to intravenously administered chemotherapeutic agents that are metabolized by CYP3A4 was higher when NEPA was coadministered than when PALO alone was coadministered in cancer patients. Compared with coadministration with PALO alone, following coadministration with NEPA, the mean Cmax and AUC of docetaxel were 49% and 35% higher, respectively; the mean Cmax and AUC of etoposide were increased by 10% and 28%, respectively; and the mean Cmax and AUC for cyclophosphamide were 27% and 20% higher.34 However, one study of NEPA reported no evidence of cyclophosphamide toxicity35 and reported safety results from the Phase 2 and Phase 3 studies to date are not suggestive of any clinically significant interactions.

Although not the focus of these studies, the data suggest that clinically significant DDIs between PALO and CYP3A4 inhibitors or inducers are unlikely. This is consistent with the known DDI profile of PALO,20 and with the generally low potential for clinically significant CYP-mediated DDIs with 5-HT3 RAs overall. Like PALO,20 other 5-HT3 RAs do not appear to significantly inhibit or induce CYP isoenzymes, and coadministration with CYP inducers or inhibitors does not seem to result in clinically significant changes in PKs; the latter may be due, in part, to the fact that these drugs have metabolic pathways that involve multiple CYP isoenzymes (PALO: CYP2D6 (primarily), CYP3A4, and CYP1A2; ondansetron: CYP3A4 (primarily), CYP1A2, and CYP2D6;36 dolasetron: CYP2D6, CYP3A;37 granisetron: CYP3A4 (major metabolic pathway) and CYP1A1).38,39

While the potential for clinically significant DDIs may differ depending on the specific drugs/metabolic pathways involved, the DDI profile of NEPA seems to be consistent with other 5HT3-RA and NK1-RA antiemetics. Nevertheless, the potential for PK DDIs may influence the choice of antiemetic therapy on an individual patient basis.

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JJN is a member of the Eisai and the Merck Speakers Bureaus; TS, SC, CL, and GR are employees of Helsinn Healthcare SA; DC is a former employee of Eisai Inc.; and KK is currently an employee of Eisai Inc.

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References
1. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology (NCCN Guidelines®): anti-emesis. Version 1.2014. Fort Washington, PA: National Comprehensive Cancer Network, 2013.
2. Basch E, Prestrud AA, Hesketh PJ, et al. Antiemetic use in oncology: updated guideline recommendations from ASCO. *Am Soc Clin Oncol Educ Book* 2012; 32: 532–540.

3. Gralla RJ, Roila F, Tonato M, et al. MASCC/ESMO antiemetic guideline 2013, http://www.mascc.org/assets/Guidelines-Tools/masco_antiemetic_english_2014.pdf (accessed 6 September 2013).

4. Navari RM. Management of chemotherapy-induced nausea and vomiting: focus on newer agents and new uses for older agents. *Drugs* 2013; 73: 249–262.

5. Rojas C, Raje M, Tsukamoto T, et al. Molecular mechanisms of 5-HT3 and NK1 receptor antagonists in prevention of emesis. *Eur J Pharmacol* 2014; 722: 26–37.

6. Dos Santos LV, Souza FH, Brunetto AT, et al. Neurokinin-1 receptor antagonists for chemotherapy-induced nausea and vomiting: a systematic review. *J Natl Cancer Inst* 2012; 104: 1280–1292.

7. Rizzi A, Campi B, Camarda V, et al. In vitro and in vivo pharmacological characterization of the novel NK1 receptor selective antagonist netupitant. *Peptides* 2012; 37: 86–97.

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

9. 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: 193–199.

10. Rojas C, Li Y, Zhang J, et al. The antiemetic 5-HT3 receptor antagonist palonosetron inhibits substance P-mediated responses in vitro and in vivo. *J Pharmacol Exp Ther* 2010; 335: 362–368.

11. Schwartzberg L, Barbour SY, Morrow GR, et al. Pooled analysis of phase III clinical studies of palonosetron versus ondansetron, dolasetron, and granisetron in the prevention of chemotherapy-induced nausea and vomiting (CINV). *Support Care Cancer* 2014; 22: 469–477.

12. Popovic M, Warr DG, Deangelis C, et al. Efficacy and safety of palonosetron for the prophylaxis of chemotherapy-induced nausea and vomiting (CINV): a systematic review and meta-analysis of randomized controlled trials. *Support Care Cancer* 2014; 22: 1685–1697.

13. Stathis M, Pietra C, Rojas C, et al. Inhibition of substance P-mediated responses in NG108-15 cells by netupitant and palonosetron exhibit synergistic effects. *Eur J Pharmacol* 2012; 689: 25–30.

14. Thomas AG, Stathis M, Rojas C, et al. Netupitant and palonosetron trigger NK1 receptor internalization in NG108-15 cells. *Exp Brain Res* 2014; 232: 2637–2644.

15. Aapro M, Rugo H, Rossi G, et al. A randomized phase III study evaluating the efficacy and safety of NEPA, a fixed-dose combination of netupitant and palonosetron, for prevention of chemotherapy-induced nausea and vomiting following moderately emetogenic chemotherapy. *Ann Oncol* 2014; 25: 1328–1333.

16. 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; 25: 1333–1339.

17. 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; 25: 1340–1346.

18. Aapro MS, Karthaus M, Schwartzberg S, 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 [abstract]. *J Clin Oncol* 2014; 32(suppl 5s): 9502.

19. Fabi A and Malaguti P. An update on palonosetron hydrochloride for the treatment of radio/chemotherapy-induced nausea and vomiting. *Expert Opin Pharmacother* 2013; 14: 629–641.

20. Eisai. Aloxi® (palonosetron HCl) injection [prescribing information]. Woodcliff Lake, NJ: Eisai Inc, 2013.

21. Calcagnile S, Lanzarotti C, Rossi G, et al. Effect of netupitant, a highly selective NK1 receptor antagonist, on the pharmacokinetics of palonosetron and impact of the fixed dose combination of netupitant and palonosetron when coadministered with ketoconazole, rifampicin, and oral contraceptives. *Supportive Care Cancer* 2013; 21: 2879–2887.

22. Giuliano C, Lovati E, Funk C, et al. In vitro drug-drug interaction studies with the antiemetic drug netupitant and its major metabolites M1 and M2, involving several human cytochrome P450 isoenzymes [abstract]. *Ann Oncol* 2012; 23(suppl 9): ix520.

23. Baumann S, Tilola SO, Spinielli T, et al. A phase I study evaluating the potential drug interaction between netupitant and digoxin [abstract]. *Supportive Care Cancer* 2012; 20(suppl 1): S82.

24. Lanzarotti C and Rossi G. Effect of netupitant, a highly selective NK1 receptor antagonist, on the pharmacokinetics of midazolam, erythromycin, and dexamethasone. *Supportive Care Cancer* 2013; 21: 2783–2791.

25. Lin JH and Yamazaki M. Role of P-glycoprotein in pharmacokinetics: clinical implications. *Clin Pharmacokinet* 2003; 42: 59–98.

26. Feuring M, Lee Y, Orlowski LH, et al. Lack of effect of aprepitant on cytochrome P450 3A4 is the major enzyme involved in the metabolism of the substance P receptor antagonist aprepitant. *Drug Metab Dispos* 2004; 32: 1287–1292.

27. Shah AK, Hunt TL, Gallagher SC, et al. Pharmacokinetics of palonosetron in combination with aprepitant in healthy volunteers. *Curr Med Res Opin* 2005; 21: 595–601.

28. Sanchez RI, Wang RW, Newton DJ, et al. Cytochrome P450 3A4 is the major enzyme involved in the metabolism of the substance P receptor antagonist aprepitant. *Drug Metab Dispos* 2004; 32: 1287–1292.

29. Merck. EMEND (aprepitant) capsules, for oral use [prescribing information]. Whitehouse Station, NJ: Merck & Co, 2013.

30. Majumdar AK, McCrea JB, Panebianco DL, et al. Effects of aprepitant on cytochrome P450 3A4 activity
using midazolam as a probe. Clin Pharmacol Ther 2003; 74: 150–156.
31. Aapro MS and Walko CM. Aprepitant: drug-drug interac-
tions in perspective. Ann Oncol 2010; 21: 2316–2323.
32. McCrea JB, Majumdar AK, Goldberg MR, et al. Effects of
the neurokinin1 receptor antagonist aprepitant on the
pharmacokinetics of dexamethasone and methylprednis-
lone. Clin Pharmacol Ther 2003; 74: 17–24.
33. Shadle CR, Lee Y, Majumdar AK, et al. Evaluation of
potential inductive effects of aprepitant on cytochrome
P450 3A4 and 2C9 activity. J Clin Pharmacol 2004; 44:
215–223.
34. Eisai Inc. Akynzeo® (netupitant and palonosetron) [pre-
scribing information]. Woodcliff Lake, NJ: Eisai Inc, 2014.
35. Schwartzberg LOC, Cardona-Huerta S, Rizzi G, et al.
No evidence of increased cyclophosphamide toxicity
associated with the antiemetic agent NEPA, a fixed-
dose combination of netupitant and palonosetron. In:
55th annual meeting and exposition of the American
Society of Hematology. New Orleans, LA, 7–10
December 2013.
36. GlaxoSmithKline. ZOFRAN® (ondansetron hydrochlor-
ide) tablets; ZOFRAN ODT® (ondansetron) orally disin-
tegrating tablets; ZOFRAN® (ondansetron hydrochloride)
oral solution [prescribing information]. Research Triangle
Park, NC: GlaxoSmithKline, 2013.
37. sanofi-aventis US. Anzemet® (dolasetron mesylate) injec-
tion [prescribing information]. Bridgewater, NJ: sanofi-
aventis US, 2013.
38. Genentech USA. Kytril® (granisetron hydrochloride)
injection [prescribing information]. South San
Francisco, CA: Genentech USA, Inc, 2011.
39. ProStrakan Inc. Sancuso (granisetron transdermal
system) [prescribing information]. Bedminster, NJ:
ProStrakan Inc, 2008.