



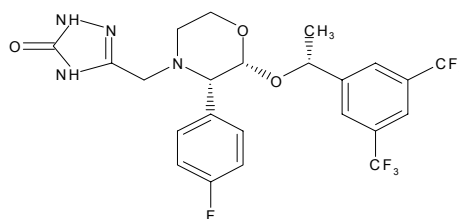
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## EMEND® (aprepitant) CAPSULES

### DESCRIPTION

EMEND® (aprepitant) is a substance P/neurokinin 1 (NK<sub>1</sub>) receptor antagonist, chemically described as 5-[[[(2*R*,3*S*)-2-[(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro-3*H*-1,2,4-triazol-3-one.

Its empirical formula is C<sub>23</sub>H<sub>21</sub>F<sub>7</sub>N<sub>4</sub>O<sub>3</sub>, and its structural formula is:



Aprepitant is a white to off-white crystalline solid, with a molecular weight of 534.43. It is practically insoluble in water. Aprepitant is sparingly soluble in ethanol and isopropyl acetate and slightly soluble in acetonitrile.

Each capsule of EMEND for oral administration contains either 80 mg or 125 mg of aprepitant and the following inactive ingredients: sucrose, microcrystalline cellulose, hydroxypropyl cellulose and sodium lauryl sulfate. The capsule shell excipients are gelatin, titanium dioxide, and may contain sodium lauryl sulfate and silicon dioxide. The 125-mg capsule also contains red ferric oxide and yellow ferric oxide.

### CLINICAL PHARMACOLOGY

#### *Mechanism of Action*

Aprepitant is a selective high-affinity antagonist of human substance P/neurokinin 1 (NK<sub>1</sub>) receptors. Aprepitant has little or no affinity for serotonin (5-HT<sub>3</sub>), dopamine, and corticosteroid receptors, the targets of existing therapies for chemotherapy-induced nausea and vomiting (CINV).

Aprepitant has been shown in animal models to inhibit emesis induced by cytotoxic chemotherapeutic agents, such as cisplatin, via central actions. Animal and human Positron Emission Tomography (PET) studies with aprepitant have shown that it crosses the blood brain barrier and occupies brain NK<sub>1</sub> receptors. Animal and human studies show that aprepitant augments the antiemetic activity of the 5-HT<sub>3</sub>-receptor antagonist ondansetron and the corticosteroid dexamethasone and inhibits both the acute and delayed phases of cisplatin-induced emesis.

#### *Pharmacokinetics*

##### *Absorption*

The mean absolute oral bioavailability of aprepitant is approximately 60 to 65% and the mean peak plasma concentration (C<sub>max</sub>) of aprepitant occurred at approximately 4 hours (T<sub>max</sub>). Oral administration of the capsule with a standard breakfast had no clinically meaningful effect on the bioavailability of aprepitant.

The pharmacokinetics of aprepitant are non-linear across the clinical dose range. In healthy young adults, the increase in AUC<sub>0-∞</sub> was 26% greater than dose proportional between 80-mg and 125-mg single doses administered in the fed state.

Following oral administration of a single 125-mg dose of EMEND on Day 1 and 80 mg once daily on Days 2 and 3, the AUC<sub>0-24hr</sub> was approximately 19.6 mcg•hr/mL and 21.2 mcg•hr/mL on Day 1 and Day 3, respectively. The C<sub>max</sub> of 1.6 mcg/mL and 1.4 mcg/mL were reached in approximately 4 hours (T<sub>max</sub>) on Day 1 and Day 3, respectively.

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### *Distribution*

Aprepitant is greater than 95% bound to plasma proteins. The mean apparent volume of distribution at steady state ( $V_{d_{ss}}$ ) is approximately 70 L in humans.

Aprepitant crosses the placenta in rats and rabbits and crosses the blood brain barrier in humans (see CLINICAL PHARMACOLOGY, *Mechanism of Action*).

### *Metabolism*

Aprepitant undergoes extensive metabolism. *In vitro* studies using human liver microsomes indicate that aprepitant is metabolized primarily by CYP3A4 with minor metabolism by CYP1A2 and CYP2C19. Metabolism is largely via oxidation at the morpholine ring and its side chains. No metabolism by CYP2D6, CYP2C9, or CYP2E1 was detected. In healthy young adults, aprepitant accounts for approximately 24% of the radioactivity in plasma over 72 hours following a single oral 300-mg dose of [ $^{14}$ C]-aprepitant, indicating a substantial presence of metabolites in the plasma. Seven metabolites of aprepitant, which are only weakly active, have been identified in human plasma.

### *Excretion*

Following administration of a single IV 100-mg dose of [ $^{14}$ C]-aprepitant prodrug to healthy subjects, 57% of the radioactivity was recovered in urine and 45% in feces. A study was not conducted with radiolabeled capsule formulation. The results after oral administration may differ.

Aprepitant is eliminated primarily by metabolism; aprepitant is not renally excreted. The apparent plasma clearance of aprepitant ranged from approximately 62 to 90 mL/min. The apparent terminal half-life ranged from approximately 9 to 13 hours.

### *Special Populations*

#### *Gender*

Following oral administration of a single 125-mg dose of EMEND, no difference in  $AUC_{0-24hr}$  was observed between males and females. The  $C_{max}$  for aprepitant is 16% higher in females as compared with males. The half-life of aprepitant is 25% lower in females as compared with males and  $T_{max}$  occurs at approximately the same time. These differences are not considered clinically meaningful. No dosage adjustment for EMEND is necessary based on gender.

#### *Geriatric*

Following oral administration of a single 125-mg dose of EMEND on Day 1 and 80 mg once daily on Days 2 through 5, the  $AUC_{0-24hr}$  of aprepitant was 21% higher on Day 1 and 36% higher on Day 5 in elderly ( $\geq 65$  years) relative to younger adults. The  $C_{max}$  was 10% higher on Day 1 and 24% higher on Day 5 in elderly relative to younger adults. These differences are not considered clinically meaningful. No dosage adjustment for EMEND is necessary in elderly patients.

#### *Pediatric*

The pharmacokinetics of EMEND have not been evaluated in patients below 18 years of age.

#### *Race*

Following oral administration of a single 125-mg dose of EMEND, the  $AUC_{0-24hr}$  is approximately 25% and 29% higher in Hispanics as compared with Whites and Blacks, respectively. The  $C_{max}$  is 22% and 31% higher in Hispanics as compared with Whites and Blacks, respectively. These differences are not considered clinically meaningful. There was no difference in  $AUC_{0-24hr}$  or  $C_{max}$  between Whites and Blacks. No dosage adjustment for EMEND is necessary based on race.

#### *Hepatic Insufficiency*

EMEND was well tolerated in patients with mild to moderate hepatic insufficiency. Following administration of a single 125-mg dose of EMEND on Day 1 and 80 mg once daily on Days 2 and 3 to patients with mild hepatic insufficiency (Child-Pugh score 5 to 6), the  $AUC_{0-24hr}$  of aprepitant was 11% lower on Day 1 and 36% lower on Day 3, as compared with healthy subjects given the same regimen. In patients with moderate hepatic insufficiency (Child-Pugh score 7 to 9), the  $AUC_{0-24hr}$  of aprepitant was 10% higher on Day 1 and 18% higher on Day 3, as compared with healthy subjects given the same regimen. These differences in  $AUC_{0-24hr}$  are not considered clinically meaningful; therefore, no dosage adjustment for EMEND is necessary in patients with mild to moderate hepatic insufficiency.

There are no clinical or pharmacokinetic data in patients with severe hepatic insufficiency (Child-Pugh score  $>9$ ) (see PRECAUTIONS).

#### *Renal Insufficiency*

A single 240-mg dose of EMEND was administered to patients with severe renal insufficiency ( $CrCl < 30$  mL/min) and to patients with end stage renal disease (ESRD) requiring hemodialysis.

In patients with severe renal insufficiency, the  $AUC_{0-\infty}$  of total aprepitant (unbound and protein bound) decreased by 21% and  $C_{max}$  decreased by 32%, relative to healthy subjects. In patients with ESRD undergoing hemodialysis, the  $AUC_{0-\infty}$  of total aprepitant decreased by 42% and  $C_{max}$  decreased by 32%.

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Due to modest decreases in protein binding of aprepitant in patients with renal disease, the AUC of pharmacologically active unbound drug was not significantly affected in patients with renal insufficiency compared with healthy subjects. Hemodialysis conducted 4 or 48 hours after dosing had no significant effect on the pharmacokinetics of aprepitant; less than 0.2% of the dose was recovered in the dialysate.

No dosage adjustment for EMEND is necessary for patients with renal insufficiency or for patients with ESRD undergoing hemodialysis.

#### *Clinical Studies*

Oral administration of EMEND in combination with ondansetron and dexamethasone (aprepitant regimen) has been shown to prevent acute and delayed nausea and vomiting associated with highly emetogenic chemotherapy including high-dose cisplatin, and nausea and vomiting associated with moderately emetogenic chemotherapy.

#### *Highly Emetogenic Chemotherapy*

In 2 multicenter, randomized, parallel, double-blind, controlled clinical studies, the aprepitant regimen (see table below) was compared with standard therapy in patients receiving a chemotherapy regimen that included cisplatin  $>50 \text{ mg/m}^2$  (mean cisplatin dose =  $80.2 \text{ mg/m}^2$ ). Of the 550 patients who were randomized to receive the aprepitant regimen, 42% were women, 58% men, 59% White, 3% Asian, 5% Black, 12% Hispanic American, and 21% Multi-Racial. The aprepitant-treated patients in these clinical studies ranged from 14 to 84 years of age, with a mean age of 56 years. 170 patients were 65 years or older, with 29 patients being 75 years or older.

Patients (N = 1105) were randomized to either the aprepitant regimen (N = 550) or standard therapy (N = 555). The treatment regimens are defined in the table below.

Treatment Regimens  
Highly Emetogenic Chemotherapy Trials

Treatment Regimen	Day 1	Days 2 to 4
Aprepitant	Aprepitant 125 mg PO Dexamethasone 12 mg PO Ondansetron 32 mg IV	Aprepitant 80 mg PO Daily (Days 2 and 3 only) Dexamethasone 8 mg PO Daily (morning)
Standard Therapy	Dexamethasone 20 mg PO Ondansetron 32 mg IV	Dexamethasone 8 mg PO Daily (morning) Dexamethasone 8 mg PO Daily (evening)

Aprepitant placebo and dexamethasone placebo were used to maintain blinding.

During these studies 95% of the patients in the aprepitant group received a concomitant chemotherapeutic agent in addition to protocol-mandated cisplatin. The most common chemotherapeutic agents and the number of aprepitant patients exposed follows: etoposide (106), fluorouracil (100), gemcitabine (89), vinorelbine (82), paclitaxel (52), cyclophosphamide (50), doxorubicin (38), docetaxel (11).

The antiemetic activity of EMEND was evaluated during the acute phase (0 to 24 hours post-cisplatin treatment), the delayed phase (25 to 120 hours post-cisplatin treatment) and overall (0 to 120 hours post-cisplatin treatment) in Cycle 1. Efficacy was based on evaluation of the following endpoints:

Primary endpoint:

- complete response (defined as no emetic episodes and no use of rescue therapy)

Other prespecified endpoints:

- complete protection (defined as no emetic episodes, no use of rescue therapy, and a maximum nausea visual analogue scale [VAS] score  $<25 \text{ mm}$  on a 0 to 100 mm scale)
- no emesis (defined as no emetic episodes regardless of use of rescue therapy)
- no nausea (maximum VAS  $<5 \text{ mm}$  on a 0 to 100 mm scale)
- no significant nausea (maximum VAS  $<25 \text{ mm}$  on a 0 to 100 mm scale)

A summary of the key study results from each individual study analysis is shown in Table 1 and in Table 2.

Table 1

Percent of Patients Receiving Highly Emetogenic Chemotherapy Responding by Treatment Group and Phase for Study 1 — Cycle 1

ENDPOINTS	Aprepitant Regimen (N = 260) <sup>†</sup> %	Standard Therapy (N = 261) <sup>†</sup> %	p-Value

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PRIMARY ENDPOINT			
Complete Response			
Overall <sup>†</sup>	73	52	<0.001
OTHER PRESPECIFIED ENDPOINTS			
Complete Response			
Acute phase <sup>§</sup>	89	78	<0.001
Delayed phase <sup>  </sup>	75	56	<0.001
Complete Protection			
Overall	63	49	0.001
Acute phase	85	75	NS*
Delayed phase	66	52	<0.001
No Emesis			
Overall	78	55	<0.001
Acute phase	90	79	0.001
Delayed phase	81	59	<0.001
No Nausea			
Overall	48	44	NS**
Delayed phase	51	48	NS**
No Significant Nausea			
Overall	73	66	NS**
Delayed phase	75	69	NS**

<sup>†</sup>N: Number of patients (older than 18 years of age) who received cisplatin, study drug, and had at least one post-treatment efficacy evaluation.

<sup>‡</sup>Overall: 0 to 120 hours post-cisplatin treatment.

<sup>§</sup>Acute phase: 0 to 24 hours post-cisplatin treatment.

<sup>||</sup>Delayed phase: 25 to 120 hours post-cisplatin treatment.

\*Not statistically significant when adjusted for multiple comparisons.

\*\*Not statistically significant.

Visual analogue scale (VAS) score range: 0 mm = no nausea; 100 mm = nausea as bad as it could be.

**Table 2**

**Percent of Patients Receiving Highly Emetogenic Chemotherapy Responding by Treatment Group and Phase for Study 2 — Cycle 1**

ENDPOINTS	Aprepitant Regimen (N = 261) <sup>†</sup> %	Standard Therapy (N = 263) <sup>‡</sup> %	p-Value
PRIMARY ENDPOINT			
Complete Response			
Overall <sup>†</sup>	63	43	<0.001
OTHER PRESPECIFIED ENDPOINTS			
Complete Response			
Acute phase <sup>§</sup>	83	68	<0.001
Delayed phase <sup>  </sup>	68	47	<0.001
Complete Protection			
Overall	56	41	<0.001
Acute phase	80	65	<0.001
Delayed phase	61	44	<0.001
No Emesis			
Overall	66	44	<0.001
Acute phase	84	69	<0.001
Delayed phase	72	48	<0.001
No Nausea			
Overall	49	39	NS*
Delayed phase	53	40	NS*
No Significant Nausea			
Overall	71	64	NS**
Delayed phase	73	65	NS**

<sup>†</sup>N: Number of patients (older than 18 years of age) who received cisplatin, study drug, and had at least one post-treatment efficacy evaluation.

<sup>‡</sup>Overall: 0 to 120 hours post-cisplatin treatment.

<sup>§</sup>Acute phase: 0 to 24 hours post-cisplatin treatment.

<sup>||</sup>Delayed phase: 25 to 120 hours post-cisplatin treatment.

\*Not statistically significant when adjusted for multiple comparisons.

\*\*Not statistically significant.

Visual analogue scale (VAS) score range: 0 mm = no nausea; 100 mm = nausea as bad as it could be.

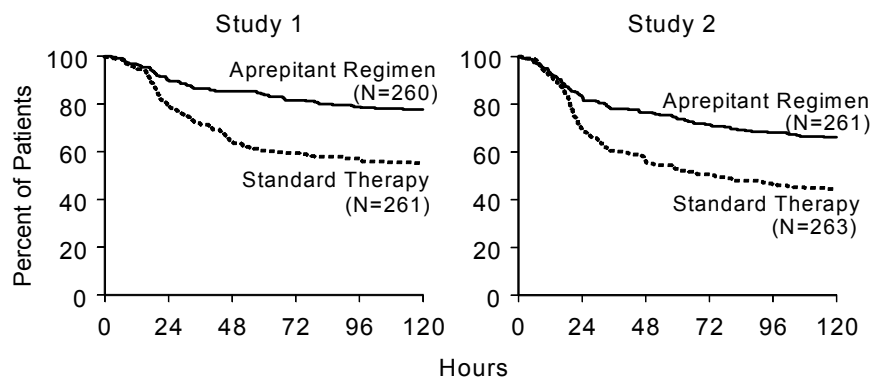
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In both studies, a statistically significantly higher proportion of patients receiving the aprepitant regimen in Cycle 1 had a complete response (primary endpoint), compared with patients receiving standard therapy. A statistically significant difference in complete response in favor of the aprepitant regimen was also observed when the acute phase and the delayed phase were analyzed separately.

In both studies, the estimated time to first emesis after initiation of cisplatin treatment was longer with the aprepitant regimen, and the incidence of first emesis was reduced in the aprepitant regimen group compared with standard therapy group as depicted in the Kaplan-Meier curves in Figure 1.

Figure 1: Percent of Patients Receiving Highly Emetogenic Chemotherapy Who Remain Emesis Free Over Time – Cycle 1

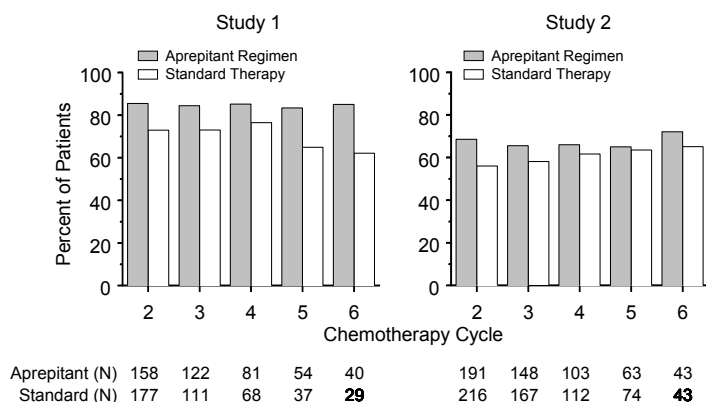


p-Value <0.001 based on a log rank test for Study 1 and Study 2; nominal p-values not adjusted for multiplicity.

**Patient-Reported Outcomes:** The impact of nausea and vomiting on patients' daily lives was assessed in Cycle 1 of both Phase III studies using the Functional Living Index–Emesis (FLIE), a validated nausea- and vomiting-specific patient-reported outcome measure. Minimal or no impact of nausea and vomiting on patients' daily lives is defined as a FLIE total score >108. In each of the 2 studies, a higher proportion of patients receiving the aprepitant regimen reported minimal or no impact of nausea and vomiting on daily life (Study 1: 74% versus 64%; Study 2: 75% versus 64%).

**Multiple-Cycle Extension:** In the same 2 clinical studies, patients continued into the Multiple-Cycle extension for up to 5 additional cycles of chemotherapy. The proportion of patients with no emesis and no significant nausea by treatment group at each cycle is depicted in Figure 2. Antiemetic effectiveness for the patients receiving the aprepitant regimen is maintained throughout repeat cycles for those patients continuing in each of the multiple cycles.

Figure 2: Proportion of Patients Receiving Highly Emetogenic Chemotherapy With No Emesis and No Significant Nausea by Treatment Group and Cycle



#### Moderately Emetogenic Chemotherapy

In a multicenter, randomized, double-blind, parallel-group, clinical study in breast cancer patients, the aprepitant regimen (see table that follows) was compared with a standard of care therapy in patients receiving a moderately emetogenic chemotherapy regimen that included cyclophosphamide 750-

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1500 mg/m<sup>2</sup>; or cyclophosphamide 500-1500 mg/m<sup>2</sup> and doxorubicin (≤60 mg/m<sup>2</sup>) or epirubicin (≤100 mg/m<sup>2</sup>).

In this study, the most common combinations were cyclophosphamide + doxorubicin (60.6%); and cyclophosphamide + epirubicin + fluorouracil (21.6%).

Of the 438 patients who were randomized to receive the aprepitant regimen, 99.5% were women. Of these, approximately 80% were White, 8% Black, 8% Asian, 4% Hispanic, and <1% Other. The aprepitant-treated patients in this clinical study ranged from 25 to 78 years of age, with a mean age of 53 years; 70 patients were 65 years or older, with 12 patients being over 74 years.

Patients (N = 866) were randomized to either the aprepitant regimen (N = 438) or standard therapy (N = 428). The treatment regimens are defined in the table that follows.

**Treatment Regimens  
Moderately Emetogenic Chemotherapy Trial**

Treatment Regimen	Day 1	Days 2 to 3
Aprepitant	Aprepitant 125 mg PO <sup>†</sup> Dexamethasone 12 mg PO <sup>‡</sup> Ondansetron 8 mg PO x 2 doses <sup>§</sup>	Aprepitant 80 mg PO Daily
Standard Therapy	Dexamethasone 20 mg PO Ondansetron 8 mg PO x 2 doses	Ondansetron 8 mg PO Daily (every 12 hours)

Aprepitant placebo and dexamethasone placebo were used to maintain blinding.

<sup>†</sup>1 hour prior to chemotherapy.

<sup>‡</sup>30 minutes prior to chemotherapy.

<sup>§</sup>30 to 60 minutes prior to chemotherapy and 8 hours after first ondansetron dose.

The antiemetic activity of EMEND was evaluated based on the following endpoints:

Primary endpoint:

Complete response (defined as no emetic episodes and no use of rescue therapy) in the overall phase (0 to 120 hours post-chemotherapy)

Other prespecified endpoints:

- no emesis (defined as no emetic episodes regardless of use of rescue therapy)
- no nausea (maximum VAS <5 mm on a 0 to 100 mm scale)
- no significant nausea (maximum VAS <25 mm on a 0 to 100 mm scale)
- complete protection (defined as no emetic episodes, no use of rescue therapy, and a maximum nausea visual analogue scale [VAS] score <25 mm on a 0 to 100 mm scale)
- complete response during the acute and delayed phases.

A summary of the key results from this study is shown in Table 3.

**Table 3**

**Percent of Patients Receiving Moderately Emetogenic Chemotherapy Responding by Treatment Group and Phase — Cycle 1**

ENDPOINTS	Aprepitant Regimen (N = 433) <sup>†</sup> %	Standard Therapy (N = 424) <sup>†</sup> %	p-Value
PRIMARY ENDPOINT			
Complete Response <sup>‡</sup>	51	42	0.015
OTHER PRESPECIFIED ENDPOINTS			
No Emesis	76	59	NS*
No Nausea	33	33	NS
No Significant Nausea	61	56	NS
No Rescue Therapy	59	56	NS
Complete Protection	43	37	NS

<sup>†</sup>N: Number of patients included in the primary analysis of complete response.

<sup>‡</sup>Overall: 0 to 120 hours post-chemotherapy treatment.

\*NS when adjusted for prespecified multiple comparisons rule; unadjusted p-value <0.001.

In this study, a statistically significantly (p=0.015) higher proportion of patients receiving the aprepitant regimen (51%) in Cycle 1 had a complete response (primary endpoint) during the overall phase compared with patients receiving standard therapy (42%). The difference between treatment groups was



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primarily driven by the “No Emesis Endpoint”, a principal component of this composite primary endpoint. In addition, a higher proportion of patients receiving the aprepitant regimen in Cycle 1 had a complete response during the acute (0-24 hours) and delayed (25-120 hours) phases compared with patients receiving standard therapy; however, the treatment group differences failed to reach statistical significance, after multiplicity adjustments.

*Patient-Reported Outcomes:* In a phase III study in patients receiving moderately emetogenic chemotherapy, the impact of nausea and vomiting on patients’ daily lives was assessed in Cycle 1 using the FLIE. A higher proportion of patients receiving the aprepitant regimen reported minimal or no impact on daily life (64% versus 56%). This difference between treatment groups was primarily driven by the “No Vomiting Domain” of this composite endpoint.

*Multiple-Cycle Extension:* Patients receiving moderately emetogenic chemotherapy were permitted to continue into the Multiple-Cycle extension of the study for up to 3 additional cycles of chemotherapy. Antiemetic effect for patients receiving the aprepitant regimen is maintained during all cycles.

## INDICATIONS AND USAGE

EMEND, in combination with other antiemetic agents, is indicated for the:

- prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy including high-dose cisplatin
- prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (see DOSAGE AND ADMINISTRATION).

## CONTRAINDICATIONS

EMEND is a moderate CYP3A4 inhibitor. EMEND should not be used concurrently with pimozide, terfenadine, astemizole, or cisapride. Inhibition of cytochrome P450 isoenzyme 3A4 (CYP3A4) by aprepitant could result in elevated plasma concentrations of these drugs, potentially causing serious or life-threatening reactions (see PRECAUTIONS, *Drug Interactions*).

EMEND is contraindicated in patients who are hypersensitive to any component of the product.

## PRECAUTIONS

### *General*

**EMEND should be used with caution in patients receiving concomitant medicinal products, including chemotherapy agents that are primarily metabolized through CYP3A4. Inhibition of CYP3A4 by aprepitant could result in elevated plasma concentrations of these concomitant medicinal products. The effect of EMEND on the pharmacokinetics of orally administered CYP3A4 substrates is expected to be greater than the effect of EMEND on the pharmacokinetics of intravenously administered CYP3A4 substrates (see PRECAUTIONS, *Drug Interactions*).**

Chemotherapy agents that are known to be metabolized by CYP3A4 include docetaxel, paclitaxel, etoposide, irinotecan, ifosfamide, imatinib, vinorelbine, vinblastine and vincristine. In clinical studies, EMEND was administered commonly with etoposide, vinorelbine, or paclitaxel. The doses of these agents were not adjusted to account for potential drug interactions.

In a separate pharmacokinetic study in patients receiving docetaxel, which is also metabolized by CYP3A4, EMEND did not influence the pharmacokinetics of docetaxel.

Due to the small number of patients in clinical studies who received the CYP3A4 substrates vinblastine, vincristine, or ifosfamide, particular caution and careful monitoring are advised in patients receiving these agents or other chemotherapy agents metabolized primarily by CYP3A4 that were not studied (see PRECAUTIONS, *Drug Interactions*).

Chronic continuous use of EMEND for prevention of nausea and vomiting is not recommended because it has not been studied and because the drug interaction profile may change during chronic continuous use.

Coadministration of EMEND with warfarin may result in a clinically significant decrease in International Normalized Ratio (INR) of prothrombin time. In patients on chronic warfarin therapy, the INR should be closely monitored in the 2-week period, particularly at 7 to 10 days, following initiation of the 3-day regimen of EMEND with each chemotherapy cycle (see PRECAUTIONS, *Drug Interactions*).

Upon coadministration with EMEND, the efficacy of hormonal contraceptives during and for 28 days following the last dose of EMEND may be reduced. Alternative or back-up methods of contraception

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should be used during treatment with EMEND and for 1 month following the last dose of EMEND (see PRECAUTIONS, *Drug Interactions*).

There are no clinical or pharmacokinetic data in patients with severe hepatic insufficiency (Child-Pugh score >9). Therefore, caution should be exercised when EMEND is administered in these patients (see CLINICAL PHARMACOLOGY, *Special Populations, Hepatic Insufficiency* and DOSAGE AND ADMINISTRATION).

#### *Information for Patients*

Physicians should instruct their patients to read the patient package insert before starting therapy with EMEND and to reread it each time the prescription is renewed.

Patients should be instructed to take EMEND only as prescribed. Patients should be advised to take their first dose (125 mg) of EMEND 1 hour prior to chemotherapy treatment.

EMEND may interact with some drugs including chemotherapy; therefore, patients should be advised to report to their doctor the use of any other prescription, non-prescription medication or herbal products.

Patients on chronic warfarin therapy should be instructed to have their clotting status closely monitored in the 2-week period, particularly at 7 to 10 days, following initiation of the 3-day regimen of EMEND with each chemotherapy cycle.

Administration of EMEND may reduce the efficacy of hormonal contraceptives. Patients should be advised to use alternative or back-up methods of contraception during treatment with EMEND and for 1 month following the last dose of EMEND.

#### *Drug Interactions*

Aprepitant is a substrate, a moderate inhibitor, and an inducer of CYP3A4. Aprepitant is also an inducer of CYP2C9.

#### *Effect of aprepitant on the pharmacokinetics of other agents*

As a moderate inhibitor of CYP3A4, aprepitant can increase plasma concentrations of coadministered medicinal products that are metabolized through CYP3A4 (see CONTRAINDICATIONS).

Aprepitant has been shown to induce the metabolism of S(-) warfarin and tolbutamide, which are metabolized through CYP2C9. Coadministration of EMEND with these drugs or other drugs that are known to be metabolized by CYP2C9, such as phenytoin, may result in lower plasma concentrations of these drugs.

EMEND is unlikely to interact with drugs that are substrates for the P-glycoprotein transporter, as demonstrated by the lack of interaction of EMEND with digoxin in a clinical drug interaction study.

**5-HT<sub>3</sub> antagonists:** In clinical drug interaction studies, aprepitant did not have clinically important effects on the pharmacokinetics of ondansetron, granisetron, or hydrodolasetron (the active metabolite of dolasetron).

#### *Corticosteroids:*

**Dexamethasone:** EMEND, when given as a regimen of 125 mg with dexamethasone coadministered orally as 20 mg on Day 1, and EMEND when given as 80 mg/day with dexamethasone coadministered orally as 8 mg on Days 2 through 5, increased the AUC of dexamethasone, a CYP3A4 substrate, by 2.2-fold on Days 1 and 5. The oral dexamethasone doses should be reduced by approximately 50% when coadministered with EMEND, to achieve exposures of dexamethasone similar to those obtained when it is given without EMEND. The daily dose of dexamethasone administered in clinical studies with EMEND reflects an approximate 50% reduction of the dose of dexamethasone (see DOSAGE AND ADMINISTRATION).

**Methylprednisolone:** EMEND, when given as a regimen of 125 mg on Day 1 and 80 mg/day on Days 2 and 3, increased the AUC of methylprednisolone, a CYP3A4 substrate, by 1.34-fold on Day 1 and by 2.5-fold on Day 3, when methylprednisolone was coadministered intravenously as 125 mg on Day 1 and orally as 40 mg on Days 2 and 3. The IV methylprednisolone dose should be reduced by approximately 25%, and the oral methylprednisolone dose should be reduced by approximately 50% when coadministered with EMEND to achieve exposures of methylprednisolone similar to those obtained when it is given without EMEND.

**Chemotherapeutic agents:** See PRECAUTIONS, *General*.

**Docetaxel:** In a pharmacokinetic study, EMEND did not influence the pharmacokinetics of docetaxel.

**Warfarin:** A single 125-mg dose of EMEND was administered on Day 1 and 80 mg/day on Days 2 and 3 to healthy subjects who were stabilized on chronic warfarin therapy. Although there was no effect of EMEND on the plasma AUC of R(+) or S(-) warfarin determined on Day 3, there was a 34% decrease in S(-) warfarin (a CYP2C9 substrate) trough concentration accompanied by a 14% decrease in the prothrombin time (reported as International Normalized Ratio or INR) 5 days after completion of dosing with EMEND. In patients on chronic warfarin therapy, the prothrombin time (INR) should be closely



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monitored in the 2-week period, particularly at 7 to 10 days, following initiation of the 3-day regimen of EMEND with each chemotherapy cycle.

**Tolbutamide:** EMEND, when given as 125 mg on Day 1 and 80 mg/day on Days 2 and 3, decreased the AUC of tolbutamide (a CYP2C9 substrate) by 23% on Day 4, 28% on Day 8, and 15% on Day 15, when a single dose of tolbutamide 500 mg was administered orally prior to the administration of the 3-day regimen of EMEND and on Days 4, 8, and 15.

**Oral contraceptives:** Aprepitant, when given once daily for 14 days as a 100-mg capsule with an oral contraceptive containing 35 mcg of ethinyl estradiol and 1 mg of norethindrone, decreased the AUC of ethinyl estradiol by 43%, and decreased the AUC of norethindrone by 8%.

In another study, a daily dose of an oral contraceptive containing ethinyl estradiol and norethindrone was administered on Days 1 through 21, and EMEND was given as a 3-day regimen of 125 mg on Day 8 and 80 mg/day on Days 9 and 10 with ondansetron 32 mg IV on Day 8 and oral dexamethasone given as 12 mg on Day 8 and 8 mg/day on Days 9, 10, and 11. In the study, the AUC of ethinyl estradiol decreased by 19% on Day 10 and there was as much as a 64% decrease in ethinyl estradiol trough concentrations during Days 9 through 21. While there was no effect of EMEND on the AUC of norethindrone on Day 10, there was as much as a 60% decrease in norethindrone trough concentrations during Days 9 through 21. The coadministration of EMEND may reduce the efficacy of hormonal contraceptives during and for 28 days after administration of the last dose of EMEND. Alternative or back-up methods of contraception should be used during treatment with EMEND and for 1 month following the last dose of EMEND.

**Midazolam:** EMEND increased the AUC of midazolam, a sensitive CYP3A4 substrate, by 2.3-fold on Day 1 and 3.3-fold on Day 5, when a single oral dose of midazolam 2 mg was coadministered on Day 1 and Day 5 of a regimen of EMEND 125 mg on Day 1 and 80 mg/day on Days 2 through 5. The potential effects of increased plasma concentrations of midazolam or other benzodiazepines metabolized via CYP3A4 (alprazolam, triazolam) should be considered when coadministering these agents with EMEND.

In another study with intravenous administration of midazolam, EMEND was given as 125 mg on Day 1 and 80 mg/day on Days 2 and 3, and midazolam 2 mg IV was given prior to the administration of the 3-day regimen of EMEND and on Days 4, 8, and 15. EMEND increased the AUC of midazolam by 25% on Day 4 and decreased the AUC of midazolam by 19% on Day 8 relative to the dosing of EMEND on Days 1 through 3. These effects were not considered clinically important. The AUC of midazolam on Day 15 was similar to that observed at baseline.

#### ***Effect of other agents on the pharmacokinetics of aprepitant***

Aprepitant is a substrate for CYP3A4; therefore, coadministration of EMEND with drugs that inhibit CYP3A4 activity may result in increased plasma concentrations of aprepitant. Consequently, concomitant administration of EMEND with strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, nefazodone, troleandomycin, clarithromycin, ritonavir, nelfinavir) should be approached with caution. Because moderate CYP3A4 inhibitors (e.g., diltiazem) result in a 2-fold increase in plasma concentrations of aprepitant, concomitant administration should also be approached with caution.

Aprepitant is a substrate for CYP3A4; therefore, coadministration of EMEND with drugs that strongly induce CYP3A4 activity (e.g., rifampin, carbamazepine, phenytoin) may result in reduced plasma concentrations of aprepitant that may result in decreased efficacy of EMEND.

**Ketoconazole:** When a single 125-mg dose of EMEND was administered on Day 5 of a 10-day regimen of 400 mg/day of ketoconazole, a strong CYP3A4 inhibitor, the AUC of aprepitant increased approximately 5-fold and the mean terminal half-life of aprepitant increased approximately 3-fold. Concomitant administration of EMEND with strong CYP3A4 inhibitors should be approached cautiously.

**Rifampin:** When a single 375-mg dose of EMEND was administered on Day 9 of a 14-day regimen of 600 mg/day of rifampin, a strong CYP3A4 inducer, the AUC of aprepitant decreased approximately 11-fold and the mean terminal half-life decreased approximately 3-fold.

Coadministration of EMEND with drugs that induce CYP3A4 activity may result in reduced plasma concentrations and decreased efficacy of EMEND.

#### ***Additional interactions***

**Diltiazem:** In patients with mild to moderate hypertension, administration of aprepitant once daily, as a tablet formulation comparable to 230 mg of the capsule formulation, with diltiazem 120 mg 3 times daily for 5 days, resulted in a 2-fold increase of aprepitant AUC and a simultaneous 1.7-fold increase of diltiazem AUC. These pharmacokinetic effects did not result in clinically meaningful changes in ECG, heart rate or blood pressure beyond those changes induced by diltiazem alone.

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*Paroxetine:* Coadministration of once daily doses of aprepitant, as a tablet formulation comparable to 85 mg or 170 mg of the capsule formulation, with paroxetine 20 mg once daily, resulted in a decrease in AUC by approximately 25% and  $C_{max}$  by approximately 20% of both aprepitant and paroxetine.

*Carcinogenesis, Mutagenesis, Impairment of Fertility*

Carcinogenicity studies were conducted in Sprague-Dawley rats and in CD-1 mice for 2 years. In the rat carcinogenicity studies, animals were treated with oral doses ranging from 0.05 to 1000 mg/kg twice daily. The highest dose produced a systemic exposure to aprepitant (plasma  $AUC_{0-24hr}$ ) of 0.7 to 1.6 times the human exposure ( $AUC_{0-24hr} = 19.6$  mcg·hr/mL) at the recommended dose of 125 mg/day. Treatment with aprepitant at doses of 5 to 1000 mg/kg twice daily caused an increase in the incidences of thyroid follicular cell adenomas and carcinomas in male rats. In female rats, it produced hepatocellular adenomas at 5 to 1000 mg/kg twice daily and hepatocellular carcinomas and thyroid follicular cell adenomas at 125 to 1000 mg/kg twice daily. In the mouse carcinogenicity studies, the animals were treated with oral doses ranging from 2.5 to 2000 mg/kg/day. The highest dose produced a systemic exposure of about 2.8 to 3.6 times the human exposure at the recommended dose. Treatment with aprepitant produced skin fibrosarcomas at 125 and 500 mg/kg/day doses in male mice.

Aprepitant was not genotoxic in the Ames test, the human lymphoblastoid cell (TK6) mutagenesis test, the rat hepatocyte DNA strand break test, the Chinese hamster ovary (CHO) cell chromosome aberration test and the mouse micronucleus test.

Aprepitant did not affect the fertility or general reproductive performance of male or female rats at doses up to the maximum feasible dose of 1000 mg/kg twice daily (providing exposure in male rats lower than the exposure at the recommended human dose and exposure in female rats at about 1.6 times the human exposure).

*Pregnancy. Teratogenic Effects: Category B.* Teratology studies have been performed in rats at oral doses up to 1000 mg/kg twice daily (plasma  $AUC_{0-24hr}$  of 31.3 mcg·hr/mL, about 1.6 times the human exposure at the recommended dose) and in rabbits at oral doses up to 25 mg/kg/day (plasma  $AUC_{0-24hr}$  of 26.9 mcg·hr/mL, about 1.4 times the human exposure at the recommended dose) and have revealed no evidence of impaired fertility or harm to the fetus due to aprepitant. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

*Nursing Mothers*

Aprepitant is excreted in the milk of rats. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for possible serious adverse reactions in nursing infants from aprepitant and because of the potential for tumorigenicity shown for aprepitant in rodent carcinogenicity studies, 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.

*Pediatric Use*

Safety and effectiveness of EMEND in pediatric patients have not been established.

*Geriatric Use*

In 2 well-controlled clinical studies, of the total number of patients (N=544) treated with EMEND, 31% were 65 and over, while 5% were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Greater sensitivity of some older individuals cannot be ruled out. Dosage adjustment in the elderly is not necessary.

## ADVERSE REACTIONS

The overall safety of aprepitant was evaluated in approximately 3800 individuals.

*Highly Emetogenic Chemotherapy*

In 2 well-controlled clinical trials in patients receiving highly emetogenic cancer chemotherapy, 544 patients were treated with aprepitant during Cycle 1 of chemotherapy and 413 of these patients continued into the Multiple-Cycle extension for up to 6 cycles of chemotherapy. EMEND was given in combination with ondansetron and dexamethasone and was generally well tolerated. Most adverse experiences reported in these clinical studies were described as mild to moderate in intensity.

In Cycle 1, clinical adverse experiences were reported in approximately 69% of patients treated with the aprepitant regimen compared with approximately 68% of patients treated with standard therapy. Table 4 shows the percent of patients with clinical adverse experiences reported at an incidence  $\geq 3\%$ .

Table 4

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**Percent of Patients Receiving Highly Emetogenic Chemotherapy With Clinical Adverse Experiences  
(Incidence  $\geq 3\%$ ) - Cycle 1**

	Aprepitant Regimen (N = 544)	Standard Therapy (N = 550)
<b>Body as a Whole/ Site Unspecified</b>		
Abdominal Pain	4.6	3.3
Asthenia/Fatigue	17.8	11.8
Dehydration	5.9	5.1
Dizziness	6.6	4.4
Fever	2.9	3.5
Mucous Membrane Disorder	2.6	3.1
<b>Digestive System</b>		
Constipation	10.3	12.2
Diarrhea	10.3	7.5
Epigastric Discomfort	4.0	3.1
Gastritis	4.2	3.1
Heartburn	5.3	4.9
Nausea	12.7	11.8
Vomiting	7.5	7.6
<b>Eyes, Ears, Nose, and Throat</b>		
Tinnitus	3.7	3.8
<b>Hemic and Lymphatic System</b>		
Neutropenia	3.1	2.9
<b>Metabolism and Nutrition</b>		
Anorexia	10.1	9.5
<b>Nervous System</b>		
Headache	8.5	8.7
Insomnia	2.9	3.1
<b>Respiratory System</b>		
Hiccups	10.8	5.6

In addition, isolated cases of serious adverse experiences, regardless of causality, of bradycardia, disorientation, and perforating duodenal ulcer were reported in highly emetogenic CINV clinical studies.

#### **Moderately Emetogenic Chemotherapy**

During Cycle 1 of a moderately emetogenic chemotherapy study, 438 patients were treated with the aprepitant regimen and 385 of these patients continued into the Multiple-Cycle extension for up to 4 cycles of chemotherapy. In Cycle 1, clinical adverse experiences were reported in approximately 73% of patients treated with the aprepitant regimen compared with approximately 75% of patients treated with standard therapy.

The adverse experience profile in the moderately emetogenic chemotherapy study was generally comparable to the highly emetogenic chemotherapy studies. Table 5 shows the percent of patients with clinical adverse experiences reported at an incidence  $\geq 3\%$ .

**Table 5**

**Percent of Patients Receiving Moderately Emetogenic Chemotherapy With Clinical Adverse Experiences (Incidence  $\geq 3\%$ ) — Cycle 1**

	Aprepitant Regimen (N = 438)	Standard Therapy (N = 428)
<b>Blood and Lymphatic System Disorders</b>		
Neutropenia	8.9	8.4
<b>Metabolism and Nutrition Disorders</b>		
Anorexia	4.3	5.8
<b>Psychiatric Disorders</b>		
Insomnia	4.1	5.6
<b>Nervous System Disorders</b>		
Dizziness	3.4	4.2
Headache	16.4	16.4
<b>Vascular Disorders</b>		
Hot Flush	3.0	1.4
<b>Respiratory, Thoracic and Mediastinal Disorders</b>		
Pharyngolaryngeal pain	3.0	2.3
<b>Gastrointestinal Disorders</b>		
Constipation	12.3	18.0
Diarrhea	5.5	6.3
Dyspepsia	8.4	4.9
Nausea	7.1	7.5
Stomatitis	5.3	4.4
<b>Skin and Subcutaneous Tissue Disorders</b>		

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Alopecia	24.0	22.2
<b>General Disorders and General Administration</b>		
<b>Site Conditions</b>		
Asthenia	3.4	3.7
Fatigue	21.9	21.5
Mucosal inflammation	2.5	3.5

Isolated cases of serious adverse experiences, regardless of causality, of dehydration, enterocolitis, febrile neutropenia, hypertension, hypoaesthesia, neutropenic sepsis, pneumonia, and sinus tachycardia were reported in the moderately emetogenic CINV clinical study.

**Highly and Moderately Emetogenic Chemotherapy**

The following additional clinical adverse experiences (incidence >0.5% and greater than standard therapy), regardless of causality, were reported in patients treated with aprepitant regimen:

**Infections and infestations:** candidiasis, herpes simplex, lower respiratory infection, pharyngitis, septic shock, upper respiratory infection, urinary tract infection.

**Neoplasms benign, malignant and unspecified (including cysts and polyps):** malignant neoplasm, non-small cell lung carcinoma.

**Blood and lymphatic system disorders:** anemia, febrile neutropenia, thrombocytopenia.

**Metabolism and nutrition disorders:** appetite decreased, diabetes mellitus, hypokalemia.

**Psychiatric disorders:** anxiety disorder, confusion, depression.

**Nervous system:** peripheral neuropathy, sensory neuropathy, taste disturbance, tremor.

**Eye disorders:** conjunctivitis.

**Cardiac disorders:** myocardial infarction, palpitations, tachycardia.

**Vascular disorders:** deep venous thrombosis, flushing, hypertension, hypotension.

**Respiratory, thoracic and mediastinal disorders:** cough, dyspnea, nasal secretion, pneumonitis, pulmonary embolism, respiratory insufficiency, vocal disturbance.

**Gastrointestinal disorders:** acid reflux, deglutition disorder, dry mouth, dysgeusia, dysphagia, eructation, flatulence, obstipation, salivation increased.

**Skin and subcutaneous tissue disorders:** acne, diaphoresis, rash.

**Musculoskeletal and connective tissue disorders:** arthralgia, back pain, muscular weakness, musculoskeletal pain, myalgia.

**Renal and urinary disorders:** dysuria, renal insufficiency.

**Reproductive system and breast disorders:** pelvic pain.

**General disorders and administrative site conditions:** edema, malaise, rigors.

**Investigations:** weight loss.

**Laboratory Adverse Experiences**

Table 6 shows the percent of patients with laboratory adverse experiences reported at an incidence ≥3% in patients receiving highly emetogenic chemotherapy.

Table 6

**Percent of Patients Receiving Highly Emetogenic Chemotherapy With Laboratory Adverse Experiences (Incidence ≥3%) - Cycle 1**

	Aprepitant Regimen (N = 544)	Standard Therapy (N = 550)
ALT Increased	6.0	4.3
AST Increased	3.0	1.3
Blood Urea Nitrogen Increased	4.7	3.5
Serum Creatinine Increased	3.7	4.3
Proteinuria	6.8	5.3

The following additional laboratory adverse experiences (incidence >0.5% and greater than standard therapy), regardless of causality, were reported in patients treated with aprepitant regimen: alkaline phosphatase increased, hyperglycemia, hyponatremia, leukocytes increased, erythrocyturia, leukocyturia.

The adverse experiences of increased AST and ALT were generally mild and transient.

The following laboratory adverse experiences were reported at an incidence ≥3% during Cycle 1 of the moderately emetogenic chemotherapy study in patients treated with the aprepitant regimen or standard therapy, respectively: decreased hemoglobin (2.3%, 4.7%) and decreased white blood cell count (9.3%, 9.0%).

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The adverse experience profiles in the Multiple-Cycle extensions for up to 6 cycles of chemotherapy were generally similar to that observed in Cycle 1.

Stevens-Johnson syndrome was reported in a patient receiving aprepitant with cancer chemotherapy in another CINV study. Angioedema and urticaria were reported in a patient receiving aprepitant in a non-CINV study.

## OVERDOSAGE

No specific information is available on the treatment of overdose with EMEND. Single doses up to 600 mg of aprepitant were generally well tolerated in healthy subjects. Aprepitant was generally well tolerated when administered as 375 mg once daily for up to 42 days to patients in non-CINV studies. In 33 cancer patients, administration of a single 375-mg dose of aprepitant on Day 1 and 250 mg once daily on Days 2 to 5 was generally well tolerated.

Drowsiness and headache were reported in one patient who ingested 1440 mg of aprepitant.

In the event of overdose, EMEND should be discontinued and general supportive treatment and monitoring should be provided. Because of the antiemetic activity of aprepitant, drug-induced emesis may not be effective.

Aprepitant cannot be removed by hemodialysis.

## DOSAGE AND ADMINISTRATION

EMEND is given for 3 days as part of a regimen that includes a corticosteroid and a 5-HT<sub>3</sub> antagonist. The recommended dose of EMEND is 125 mg orally 1 hour prior to chemotherapy treatment (Day 1) and 80 mg once daily in the morning on Days 2 and 3.

In clinical studies, the following regimen was used for the prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy:

	Day 1	Day 2	Day 3	Day 4
EMEND*	125 mg	80 mg	80 mg	none
Dexamethasone**	12 mg orally	8 mg orally	8 mg orally	8 mg orally
Ondansetron†	32 mg IV	none	none	none

\*EMEND was administered orally 1 hour prior to chemotherapy treatment on Day 1 and in the morning on Days 2 and 3.

\*\*Dexamethasone was administered 30 minutes prior to chemotherapy treatment on Day 1 and in the morning on Days 2 through 4. The dose of dexamethasone was chosen to account for drug interactions.

†Ondansetron was administered 30 minutes prior to chemotherapy treatment on Day 1.

In a clinical study, the following regimen was used for the prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy:

	Day 1	Day 2	Day 3
EMEND*	125 mg	80 mg	80 mg
Dexamethasone**	12 mg orally	none	none
Ondansetron†	2 x 8 mg orally	none	none

\*EMEND was administered orally 1 hour prior to chemotherapy treatment on Day 1 and in the morning on Days 2 and 3.

\*\*Dexamethasone was administered 30 minutes prior to chemotherapy treatment on Day 1. The dose of dexamethasone was chosen to account for drug interactions.

†Ondansetron 8-mg capsule was administered 30 to 60 minutes prior to chemotherapy treatment and one 8-mg capsule was administered 8 hours after the first dose on Day 1.

EMEND has not been studied for the treatment of established nausea and vomiting.

Chronic continuous administration is not recommended (see PRECAUTIONS).

See PRECAUTIONS, *Drug Interactions* for additional information on dose adjustment for corticosteroids when coadministered with EMEND.

Refer to the full prescribing information for coadministered antiemetic agents.

EMEND may be taken with or without food.

No dosage adjustment is necessary for the elderly.

No dosage adjustment is necessary for patients with renal insufficiency or for patients with end stage renal disease undergoing hemodialysis.

No dosage adjustment is necessary for patients with mild to moderate hepatic insufficiency (Child-Pugh score 5 to 9). There are no clinical data in patients with severe hepatic insufficiency (Child-Pugh score >9).



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#### HOW SUPPLIED

No. 3854 — 80 mg capsules: White, opaque, hard gelatin capsule with “461” and “80 mg” printed radially in black ink on the body. They are supplied as follows:

**NDC** 0006-0461-30 bottles of 30 (with desiccant)

**NDC** 0006-0461-06 unit-dose packages of 6.

No. 3855 — 125 mg capsules: Opaque, hard gelatin capsule with white body and pink cap with “462” and “125 mg” printed radially in black ink on the body. They are supplied as follows:

**NDC** 0006-0462-30 bottles of 30 (with desiccant)

**NDC** 0006-0462-06 unit-dose packages of 6.

No. 3862 — Unit-of-use tri-fold pack containing one 125 mg capsule and two 80 mg capsules.

**NDC** 0006-3862-03.


#### *Storage*

Bottles: Store at 20-25°C (68-77°F) [see USP Controlled Room Temperature]. The desiccant should remain in the original bottle.

Blisters: Store at 20-25°C (68-77°F) [see USP Controlled Room Temperature].

Rx only

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 **MERCK & CO., INC.**, Whitehouse Station, NJ 08889, USA

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