LOCAL PRODUCT CIRCULAR

Capsules
EMEND®
(aprepitant, MSD)

I. THERAPEUTIC CLASS

EMEND® (aprepitant, MSD), is a substance P neurokinin 1 (NK_1) receptor antagonist.

II. CLINICAL PHARMACOLOGY

IIa. Mechanism of Action

Aprepitant has a unique mode of action; it is a selective high affinity antagonist at human substance P neurokinin 1 (NK_1) receptors. Counter-screening assays showed that aprepitant was at least 3,000-fold selective for the NK_1 receptor over other enzyme, transporter, ion channel and receptor sites including the dopamine and serotonin receptors that are targets for existing chemotherapy induced nausea and vomiting (CINV).

NK_1-receptor antagonists have been shown pre-clinically to inhibit emesis induced by cytotoxic chemotherapeutic agents, such as cisplatin, via central actions. Preclinical and human Positron Emission Tomography (PET) studies with aprepitant have shown that it is brain penetrant and occupies brain NK_1 receptors. Preclinical studies show that aprepitant has a long duration of central activity, inhibits both the acute and delayed phases of cisplatin-induced emesis, and augments the antiemetic activity of the 5-HT_3-receptor antagonist ondansetron and the corticosteroid dexamethasone against cisplatin-induced emesis.

IIb. Pharmacokinetics

IIb-1. Absorption

The mean absolute oral bioavailability of aprepitant is approximately 60 to 65% and the mean peak plasma concentration (C_{max}) of aprepitant occurred at approximately 4 hours (T_{max}). 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 $AUC_{0-\infty}$ was 26% greater than dose proportional between 80-mg and 125-mg single doses administered in the fed state. A separate clinical study in healthy young adults demonstrated that there is no clinically important effect of food on the pharmacokinetics of a single 40-mg dose of aprepitant.

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_{0-24hr} was approximately 19.5 µg•hr/mL and 20.1 µg•hr/mL on Day 1 and Day 3, respectively. The C_{max} of 1.5 µg/mL and 1.4 µg/mL were reached in approximately 4 hours (T_{max}) on Day 1 and Day 3, respectively.

IIb-2. Distribution

Aprepitant is greater than 95% bound to plasma proteins. The geometric mean apparent volume of distribution at steady state (Vd_{ss}) is approximately 66 L in humans.

Aprepitant crosses the placenta in rats, and crosses the blood brain barrier in rats and ferrets. PET studies in humans indicate that aprepitant crosses the blood brain barrier (see CLINICAL PHARMACOLOGY, *Mechanism of Action*).

IIb-3. Metabolism

Aprepitant undergoes extensive metabolism. 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. The metabolism of aprepitant occurs largely via oxidation at the morpholine ring and its side chains. *In vitro* studies using human liver microsomes indicate that aprepitant is metabolized primarily by CYP3A4 with minor metabolism by CYP1A2 and CYP2C19, and no metabolism by CYP2D6, CYP2C9, or CYP2E1.

IIb-4. Elimination

Aprepitant is eliminated primarily by metabolism; aprepitant is not renally excreted. Following administration of a single oral 300-mg dose of [^{14}C]-aprepitant to healthy subjects, 5% of the radioactivity was recovered in urine and 86% in feces.

The apparent plasma clearance of aprepitant ranged from approximately 60 to 84 mL/min. The apparent terminal half-life ranged from approximately 9 to 13 hours.

IIb-5. Characteristics in Patients

Gender

Following oral administration of a single dose of EMEND, the $AUC_{0\text{-}24hr}$ and C_{max} for aprepitant are 9% and 17% higher, respectively, in females as compared with males. The half-life of aprepitant is approximately 25% lower in females as compared with males and its 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.

Elderly

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 $AUC_{0\text{-}24hr}$ of aprepitant was 21% higher on Day 1 and 36% higher on Day 5 in elderly (≥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 $AUC_{0\text{-}24hr}$ is approximately 27% and 31% higher in Hispanics as compared with Caucasians and Blacks, respectively. The C_{max} is 19% and 29% higher in Hispanics as compared with Caucasians and Blacks, respectively. Single dose administration of oral aprepitant in Asians resulted in a 74% and 47% increase in $AUC_{0\text{-}24hr}$ and C_{max}, respectively, as compared to Caucasians. These differences are not considered clinically meaningful. No dosage adjustment for EMEND is necessary based on race.

Body Mass Index (BMI)

Body Mass Index (BMI) had no clinically meaningful effect on the pharmacokinetics of aprepitant.

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 $AUC_{0\text{-}24hr}$ 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 $AUC_{0\text{-}24hr}$ 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 $AUC_{0\text{-}24hr}$ 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).

Renal Insufficiency

A single 240-mg dose of aprepitant 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%. 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 in patients with severe renal insufficiency or in patients with ESRD undergoing hemodialysis.

IIc. Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of single and repeated dose toxicity, genotoxicity, carcinogenic potential, and toxicity to reproduction. However, it should be noted systemic exposure in rodents was similar or even lower than therapeutic exposure in humans. In particular, although no adverse effects were noted in reproduction studies at human exposure levels, the animal exposures are not sufficient to make an adequate risk assessment in men.

III. INDICATIONS

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 (see DOSAGE AND ADMINISTRATION)
- moderately emetogenic cancer chemotherapy (see DOSAGE AND ADMINISTRATION).

IV. DOSAGE AND ADMINISTRATION

PREVENTION OF CHEMOTHERAPY INDUCED NAUSEA AND VOMITING

EMEND is given for 3 days as part of a regimen that includes a corticosteroid and a 5-HT_3 antagonist.

The package insert for the co-administered 5-HT_3 antagonist must be consulted prior to initiation of treatment with EMEND.

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
5-HT_3 antagonist	See the package insert for the selected 5-HT_3 antagonist for appropriate	none	none	none

	dosing information.			

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

Recommended dosing 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
5-HT_3 antagonist	See the package insert for the selected 5-HT_3 antagonist for appropriate dosing information.	none	none

**Dexamethasone should be administered 30 minutes prior to chemotherapy treatment on Day 1. The dose of dexamethasone accounts for drug interactions.

GENERAL INFORMATION

See DRUG INTERACTIONS for additional information on the administration of EMEND with corticosteroids.

Refer to the full prescribing information for coadministered antiemetic agents.

EMEND may be taken with or without food.

No dosage adjustment is necessary based on age, gender, race or Body Mass Index (BMI)

No dosage adjustment is necessary for patients with severe renal insufficiency (creatinine clearance <30 mL/min) 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).

V. CLINICAL STUDIES

PREVENTION OF CHEMOTHERAPY INDUCED NAUSEA AND VOMITING

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 and moderately emetogenic chemotherapy in well-controlled clinical studies.

Highly Emetogenic Chemotherapy

In 2 multicenter, randomized, parallel, double-blind, controlled clinical studies, the aprepitant regimen was compared with standard therapy in 1094 patients receiving a chemotherapy regimen that included cisplatin ≥70 mg/m^2. Some patients also received additional chemotherapeutic agents such as gemcitabine, etoposide, fluorouracil, vinorelbine tartrate, doxorubicin, cyclophosphamide, paclitaxel, or docetaxel. The aprepitant regimen consisted of EMEND 125 mg on Day 1 and 80 mg/day on Days 2 and 3 in combination with ondansetron 32 mg IV on Day 1 and dexamethasone 12 mg on Day 1 and 8 mg once daily on Days 2 through 4. Standard therapy consisted of placebo in combination with ondansetron 32 mg IV on Day 1 and dexamethasone 20 mg on Day 1 and 8 mg twice daily on Days 2 through 4. Although a 32 mg IV dose of ondansetron was used in clinical trials, this may no longer be the currently recommended dose. See the package insert for the selected 5-HT$_3$ antagonist for appropriate dosing information.

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 composite measures:

- complete response (defined as no emetic episodes and no use of rescue therapy)
- complete protection (defined as no emetic episodes, no use of rescue therapy, and a maximum nausea visual analogue scale [VAS] score <25 mm)
- impact of nausea and vomiting on daily life (Functional Living Index-Emesis [FLIE] total score >108).

Efficacy was also based on the following individual efficacy measures:

- no emesis (defined as no emetic episodes regardless of use of rescue therapy)
- no significant nausea (maximum VAS <25 mm).

The results were evaluated for each individual study and for the 2 studies combined.

A summary of the key study results from the combined analysis is shown in Table 1.

Table 1

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

COMPOSITE MEASURES	Aprepitant Regimen* (N = 521)† %	Standard Therapy** (N = 524) † %	p-Value
Complete Response (no emesis and no rescue therapy)			
Overall‡	67.7	47.8	<0.001
Acute phase§	86.0	73.2	<0.001
Delayed phase¶	71.5	51.2	<0.001
Complete Protection (no emesis, no rescue therapy and maximum nausea VAS¶ <25 mm)			
Overall	59.5	44.9	<0.001
			<0.001
Acute phase	82.4	69.6	<0.001
Delayed phase	63.7	47.8	

No Impact on Daily Life (Functional Living Index-Emesis [FLIE] total score >108)			
Overall	74.4	63.9	<0.001

INDIVIDUAL MEASURES

No Emesis (no emetic episodes regardless of use of rescue therapy)			
Overall	71.9	49.7	<0.001
Acute phase	86.8	74.0	<0.001
Delayed phase	76.2	53.5	<0.001
No Significant Nausea (maximum VAS <25 mm)			
Overall	72.1	64.9	0.014
Delayed phase	74.0	66.9	0.013

*Aprepitant Regimen: EMEND 125 mg orally on Day 1 and 80 mg orally once daily on Days 2 and 3 plus ondansetron 32 mg IV on Day 1 and dexamethasone 12 mg orally on Day 1 and 8 mg orally once daily on Days 2 to 4.

**Standard therapy: Placebo plus ondansetron 32 mg IV on Day 1 plus dexamethasone 20 mg orally on Day 1 and 8 mg orally twice daily on Days 2 to 4.

†N: Number of patients who received cisplatin, study drug, and had at least one post-treatment efficacy evaluation.

‡Overall: 0 to 120 hours post-cisplatin treatment.

§Acute phase: 0 to 24 hours post-cisplatin treatment.

¶Delayed phase: 25 to 120 hours post-cisplatin treatment.

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

In the combined analysis, a statistically significantly higher proportion of patients receiving the aprepitant regimen in Cycle 1 had a complete response and had complete protection, compared with patients receiving standard therapy. A statistically significant difference in complete response and complete protection was observed in patients receiving the

aprepitant regimen during the acute phase and the delayed phase in Cycle 1, compared with patients receiving standard therapy. These findings were also observed in each of the 2 individual studies.

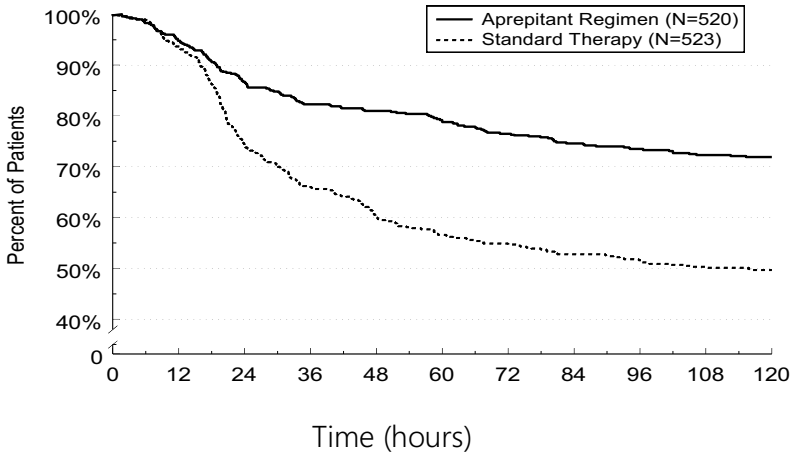
In the combined analysis, a statistically significantly higher proportion of patients receiving the aprepitant regimen in Cycle 1 had no emesis, compared with patients receiving standard therapy. A statistically significant difference in no emesis was observed in patients receiving the aprepitant regimen during the acute and delayed phases in Cycle 1, compared with patients receiving standard therapy. These findings were also observed in each of the 2 individual studies.

Furthermore, in the combined analysis, regardless of use of rescue therapy, a statistically significantly higher proportion of patients receiving the aprepitant regimen in Cycle 1 had no significant nausea overall and no significant nausea during the delayed phase, compared with patients receiving standard therapy.

The impact of nausea and vomiting on patients' daily lives was assessed using the Functional Living Index-Emesis (FLIE), a validated patient-reported outcome measure. In the combined analysis, a statistically significantly higher proportion of patients receiving the aprepitant regimen in Cycle 1 reported no impact of nausea and vomiting on daily life, as measured by a FLIE total score >108, compared with patients receiving standard therapy. These findings were also observed in each of the 2 individual studies.

In the combined analysis, the estimated time to first emesis after initiation of cisplatin treatment was significantly ($p<0.001$) 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 Figure 1.

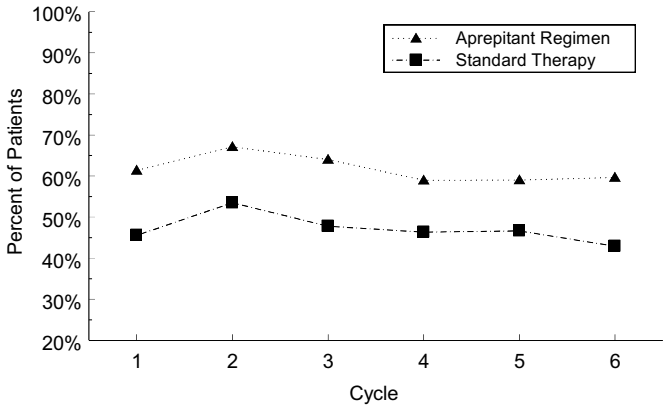
Figure 1: Percent of Patients Receiving Highly Emetogenic Chemotherapy Who Remain Emesis Free Over Time—Cycle 1



Aprepitant Regimen: EMEND 125 mg orally on Day 1 and 80 mg orally once daily on Days 2 and 3 plus ondansetron 32 mg IV on Day 1 and dexamethasone 12 mg orally on Day 1 and 8 mg orally once daily on Days 2 to 4.
Standard Therapy: Placebo plus ondansetron 32 mg IV on Day 1 plus dexamethasone 20 mg orally on Day 1 and 8 mg orally twice daily on Days 2 to 4.

Multiple-Cycle Extension: In the same 2 clinical studies, 851 patients continued into the Multiple-Cycle extension for up to 6 cycles of chemotherapy. The efficacy of the aprepitant regimen was maintained during all cycles. The response rates for the endpoint of no emesis and no significant nausea over the 6 cycles of chemotherapy following initiation of cisplatin therapy from the combined analysis are depicted in Figure 2. During Cycles 2 to 6, the endpoint of no significant nausea was determined by response to a direct question rather than by use of the VAS employed in Cycle 1.

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



	N	N	N	N	N	N
Aprepitant Regimen:	516	290	216	140	86	60
Standard Therapy:	522	274	182	115	65	43

Aprepitant Regimen: EMEND 125 mg orally on Day 1 and 80 mg orally once daily on Days 2 and 3 plus ondansetron 32 mg IV on Day 1 and dexamethasone 12 mg orally on Day 1 and 8 mg orally once daily on Days 2 to 4.
Standard Therapy: Placebo plus ondansetron 32 mg IV on Day 1 plus dexamethasone 20 mg orally on Day 1 and 8 mg orally twice daily on Days 2 to 4.

Moderately Emetogenic Chemotherapy

In a multicenter, randomized, double-blind, parallel-group, clinical study, the aprepitant regimen was compared with standard therapy in 866 breast cancer patients receiving a chemotherapy regimen that included cyclophosphamide 750-1500 mg/m^2; or cyclophosphamide 500-1500 mg/m^2 and doxorubicin (≤60 mg/m^2) or epirubicin (≤ 100 mg/m^2). Some patients also received other chemotherapeutic agents such as fluorouracil, methotrexate, docetaxel or paclitaxel. The aprepitant regimen consisted of EMEND 125 mg on Day 1 and 80 mg/day on Days 2 and 3 in combination with ondansetron 8 mg orally twice on Day 1 plus dexamethasone 12 mg orally on Day 1. Standard therapy

consisted of placebo in combination with ondansetron 8 mg orally (twice on Day 1, and every 12 hours on Days 2 and 3) plus dexamethasone 20 mg orally on Day 1.

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

- complete response (defined as no emetic episodes and no use of rescue therapy)
- impact of nausea and vomiting on daily life (Functional Living Index-Emesis [FLIE] total score >108).

Efficacy was also based on the following individual efficacy measures:

- no emesis (defined as no emetic episodes regardless of use of rescue therapy)
- no rescue therapy.

A summary of the key study results is shown in Table 2.

Table 2

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

COMPOSITE MEASURES	Aprepitant Regimen* (N = 433)[†] %	Standard Therapy** (N = 424)[†] %	p-Value
Complete Response (no emesis and no rescue therapy)			
Overall[‡]	51	42	0.015
Acute phase[§]	76	69	0.034
Delayed phase[‖]	55	49	0.064
No Impact on Daily Life (Functional Living Index-Emesis [FLIE] total score >108)			
Overall	64	56	0.019

INDIVIDUAL MEASURES			
No Emesis			
Overall	76	59	<0.001
Acute phase	88	77	<0.001
Delayed phase	81	69	<0.001
No Rescue Therapy			
Overall	59	56	0.480
Acute phase	83	80	0.366
Delayed phase	63	60	0.407

*Aprepitant Regimen: EMEND 125 mg orally on Day 1 and 80 mg orally on Days 2 and 3 plus ondansetron 8 mg orally twice on Day 1 plus dexamethasone 12 mg orally on Day 1.

**Standard Therapy: Placebo plus ondansetron 8 mg orally (twice on Day 1 and every 12 hours on Days 2 and 3) plus dexamethasone 20 mg orally on Day 1.

[†]N: Number of patients included in the primary analysis of complete response.

[‡]Overall: 0 to 120 hours post-chemotherapy treatment.

[§]Acute phase: 0 to 24 hours post-chemotherapy treatment.

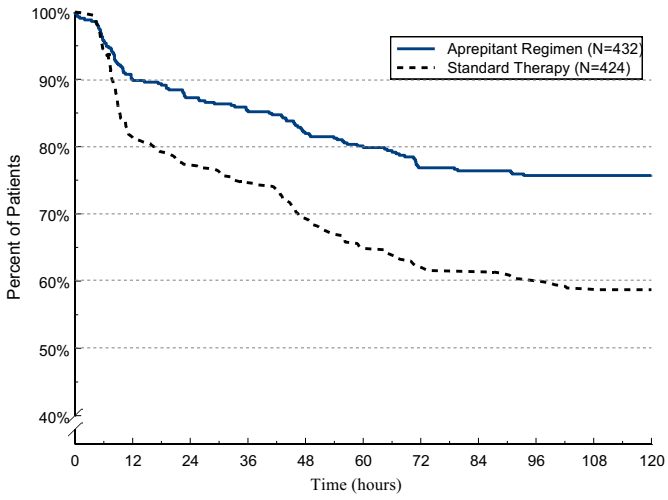
[‖]Delayed phase: 25 to 120 hours post-chemotherapy treatment.

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 unadjusted absolute difference in complete response (8.3%) represents a 20% relative improvement (relative risk ratio = 1.2, aprepitant regimen over standard therapy). A higher proportion of patients receiving the aprepitant regimen in Cycle 1 had a complete response during the acute and delayed phases compared with patients receiving standard therapy.

In this study, the estimated time to first emesis after initiation of chemotherapy treatment was significantly (p<0.001) longer with the aprepitant regimen, and the incidence of first

emesis was reduced in the aprepitant regimen group compared with the standard therapy group as depicted in Figure 3.

Figure 3: Percent of Patients Receiving Moderately Emetogenic Chemotherapy Who Remain Emesis Free Over Time—Cycle 1

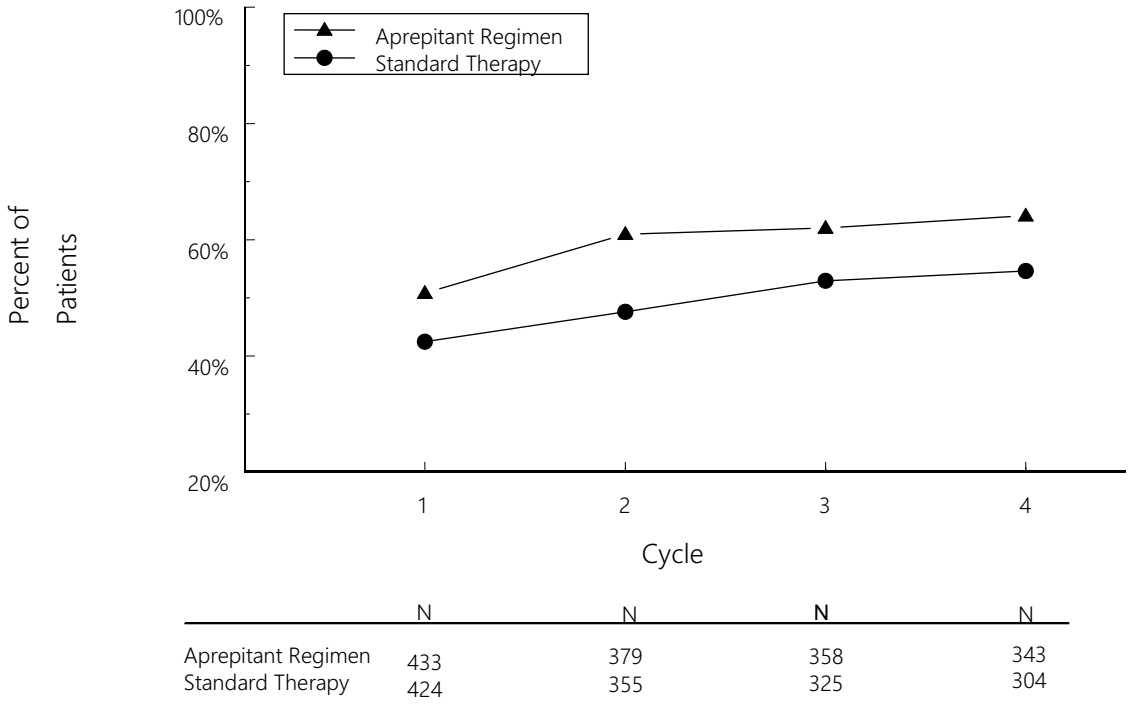


Aprepitant Regimen: EMEND 125 mg orally on Day 1 and 80 mg orally on Days 2 and 3 plus ondansetron 8 mg orally twice on Day 1 plus dexamethasone 12 mg orally on Day 1. Standard Therapy: Placebo plus ondansetron 8 mg orally (twice on Day 1 and every 12 hours on Days 2 and 3) plus dexamethasone 20 mg orally on Day 1.

In this study, a statistically significantly higher proportion of patients receiving the aprepitant regimen in Cycle 1 reported no impact of nausea and vomiting on daily life, as measured by a FLIE total score >108, compared with patients receiving standard therapy.

Multiple-Cycle Extension: A total of 744 patients receiving moderately emetogenic cancer chemotherapy continued into the Multiple-Cycle extension for up to 4 cycles of chemotherapy. The efficacy of the aprepitant regimen was maintained during all cycles. The response rates are depicted in Figure 4.

Figure 4: Percent of Patients Receiving Moderately Emetogenic Chemotherapy With No Emesis and No Rescue Therapy by Treatment Group and Cycle



Aprepitant Regimen: EMEND 125 mg orally on Day 1 and 80 mg orally on Days 2 and 3 plus ondansetron 8 mg orally twice on Day 1 plus dexamethasone 12 mg orally on Day 1. Standard Therapy: Placebo plus ondansetron 8 mg orally (twice on Day 1 and every 12 hours on Days 2 and 3) plus dexamethasone 20 mg orally on Day 1.

In a second multicenter, randomized, double-blind, parallel-group, clinical study, the aprepitant regimen was compared with standard therapy in 848 patients receiving a chemotherapy regimen that included any IV dose of oxaliplatin, carboplatin, epirubicin, idarubicin, ifosfamide, irinotecan, daunorubicin, doxorubicin; cyclophosphamide IV (<1500 mg/m^2); or cytarabine IV (>1 g/m^2). Patients who were randomized to receive the aprepitant regimen consisted of 76% women and 24% men. Patients receiving the aprepitant regimen were receiving chemotherapy for a variety of tumor types including 52% with breast cancer, 21% with gastrointestinal cancers including colorectal cancer, 13% with lung cancer and 6% with gynecological cancers. The aprepitant regimen consisted of EMEND 125 mg on Day 1 and 80 mg/day on Days 2 and 3 in combination with ondansetron

8 mg orally twice on Day 1 plus dexamethasone 12 mg orally on Day 1. Standard therapy consisted of placebo in combination with ondansetron 8 mg orally (twice on Day 1, and every 12 hours on Days 2 and 3) plus dexamethasone 20 mg orally on Day 1.

The antiemetic activity of EMEND was evaluated during the overall phase (0 to 120 hours post-chemotherapy treatment) in Cycle 1. Efficacy was based on the evaluation of the following endpoints:

Primary endpoint:

- no vomiting in the overall period (0 to 120 hours post-chemotherapy)

Other prespecified endpoints:

- complete response (defined as no vomiting and no use of rescue therapy) in the overall period (0 to 120 hours post-chemotherapy)
- time to first vomiting episode overall (0 to 120 hours post-chemotherapy)
- no vomiting – Acute (0 to 24 hours following initiation of chemotherapy infusion) and Delayed (25 to 120 hours following initiation of chemotherapy infusion)
- complete response - Acute and Delayed, as defined above
- no use of rescue therapy – Overall, Acute, and Delayed, as defined above
- no Impact on Daily Life (Functional Living Index-Emesis [FLIE] total score >108) – Overall, as defined above
- no vomiting and no significant nausea (VAS <25 mm) – Overall, as defined above

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

Table 3

Percent of Patients Receiving Moderately Emetogenic Chemotherapy Responding by Treatment Group and Phase for Study 2 – Cycle 1

ENDPOINTS	Aprepitant Regimen* (N = 430)[†] %	Standard Therapy** (N = 418)[†] %	p-Value[‡]
PRIMARY ENDPOINT			
No Vomiting			
Overall[§]	76	62	<0.0001
KEY SECONDARY ENDPOINT			
Complete Response[¶]			
Overall[§]	69	56	0.0003
OTHER SECONDARY ENDPOINTS			
No Vomiting			
Acute phase[#]	92	84	0.0002
Delayed phase[Þ]	78	67	0.0005
No Impact on Daily Life (FLIE total score >108)			
Overall	73	66	0.035
Complete Response			
Acute phase	89	80	0.0005
Delayed phase	71	61	0.0042
No Use of Rescue Therapy			
Overall	81	75	0.0427[ß]

Acute phase			0.0179[ß]
Male[à]	97	100	
Female[à]	95	88	
Delayed phase	84	79	0.0922[ß]
No Vomiting and No Significant Nausea (VAS <25 mm)			
Overall	65	53	0.0011

*Aprepitant Regimen: EMEND 125 mg orally on Day 1 and 80 mg orally on Days 2 and 3 plus ondansetron 8 mg orally twice on Day 1 plus dexamethasone 12 mg orally on Day 1.

**Standard Therapy: Placebo plus ondansetron 8 mg orally (twice on Day 1 and every 12 hours on Days 2 and 3) plus dexamethasone 20 mg orally on Day 1.

[†]N = Number of patients who received chemotherapy treatment, study drug, and had at least one post-treatment efficacy evaluation.

[‡]Hochberg's procedure was used as a multiplicity adjustment when testing secondary endpoints for significance.

[§]Overall: 0 to 120 hours post-chemotherapy treatment.

[¶]Complete Response = No Vomiting with no rescue therapy

[#] Acute phase: 0 to 24 hours following initiation of chemotherapy infusion.

[Þ] Delayed phase: 25 to 120 hours following initiation of chemotherapy infusion.

[ß]Not statistically significant.

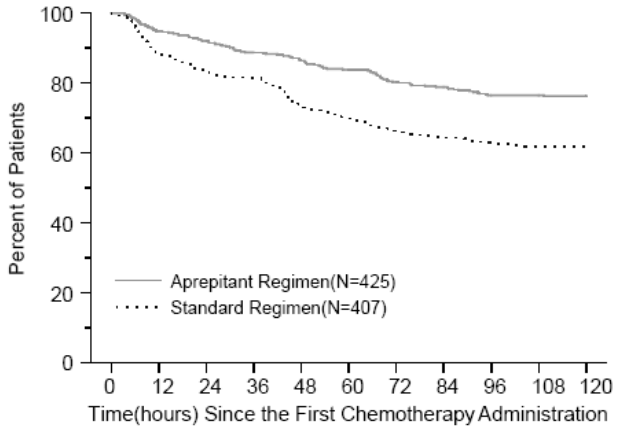
[à]Data are shown separately for males and females per prespecified analytic plan

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

In this study, a statistically significantly ($p<0.0001$) higher proportion of patients receiving the aprepitant regimen (76%) in Cycle 1 had no vomiting (primary endpoint) during the overall phase compared with patients receiving standard therapy (62%). In addition, a higher proportion of patients receiving the aprepitant regimen in Cycle 1 had a complete response in the overall phase (0-120 hours) compared with patients receiving standard therapy. Aprepitant was numerically superior versus standard therapy regardless of age, gender, or tumor type (breast, gastrointestinal, lung or other) as assessed by the No Vomiting and Complete Response endpoints.

In this study, the estimated time to first vomiting after initiation of chemotherapy treatment was longer with the aprepitant regimen, and the incidence was reduced in the aprepitant regimen group compared with standard therapy group as depicted in the Kaplan-Meier curves in Figure 5.

Figure 5: Kaplan-Meier Curves for Time to First Vomiting Episode
From Start of Chemotherapy Administration in the Overall Phase – Cycle 1
(Full Analysis Set Patient Population)



In this study, a statistically significantly higher proportion of patients receiving the aprepitant regimen in Cycle 1 reported no impact of nausea and vomiting on daily life, as measured by a FLIE total score >108, compared with patients receiving standard therapy.

VI. CONTRAINDICATIONS

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

EMEND should not be used concurrently with pimozide, terfenadine, astemizole, or cisapride. Dose-dependent 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 DRUG INTERACTIONS).

VII. PRECAUTIONS

EMEND, a dose-dependent inhibitor of CYP3A4, should be used with caution in patients receiving concomitant orally administered medicinal products that are primarily metabolized through CYP3A4; some chemotherapy agents are metabolized by CYP3A4 (see DRUG INTERACTIONS). Caution is advised both during and up to 2 weeks after the end of treatment with EMEND due to the inhibitory and inductive effects of aprepitant on CYP3A4 substrates. Moderate inhibition of CYP3A4 by aprepitant, 125 mg/80 mg regimen, could result in elevated plasma concentrations of these concomitant medicinal products administered orally (see DRUG INTERACTIONS). The effect of EMEND on the pharmacokinetics of orally administered CYP3A4 substrates is greater than the effect of EMEND on the pharmacokinetics of intravenously administered CYP3A4 substrates (see DRUG INTERACTIONS).

Coadministration of EMEND with ergot alkaloid derivatives, which are CYP3A4 substrates, may result in elevated plasma concentrations of these medicinal products. Therefore, caution is advised due to potential risk of ergot-related toxicity.

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 DRUG INTERACTIONS).

The efficacy of hormonal contraceptives during and for 28 days after administration of EMEND may be reduced. Alternative or back-up methods of contraception should be used during treatment with EMEND and for 1 month following the last dose of EMEND (*see* DRUG INTERACTIONS).

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

VIII. PREGNANCY

There are no adequate and well-controlled studies in pregnant women. EMEND should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and the fetus.

IX. NURSING MOTHERS

Aprepitant is excreted in the milk of lactating 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 possible adverse effects of EMEND on nursing infants, 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.

X. PEDIATRIC USE

Safety and effectiveness of EMEND in pediatric patients have not been established. Use in patients under 18 years of age is not recommended.

XI. USE IN THE ELDERLY

In clinical studies, the efficacy and safety of EMEND in the elderly (≥65 years) were comparable to those seen in younger patients (<65 years). No dosage adjustment is necessary in elderly patients.

XII. DRUG INTERACTIONS

Aprepitant is a substrate, a weak-to-moderate (dose-dependent) 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 (125 mg/80 mg) inhibitor of CYP3A4, aprepitant can increase plasma concentrations of orally coadministered medicinal products that are metabolized through CYP3A4. Aprepitant (125 mg/80 mg) can increase plasma concentrations of intravenously coadministered medicinal products metabolized through CYP3A4 to a lesser extent.

EMEND should not be used concurrently with pimozide, terfenadine, astemizole, or cisapride. Dose-dependent inhibition of CYP3A4 by aprepitant could result in elevated plasma concentrations of these drugs, potentially causing serious or life-threatening reactions (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$_3$ 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 usual oral dexamethasone doses should be reduced by approximately 50% when coadministered with EMEND (125 mg/80 mg regimen), to achieve exposures of dexamethasone similar to those

obtained when it is given without EMEND. The daily dose of dexamethasone administered in clinical chemotherapy induced nausea and vomiting 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 1.3-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 usual IV methylprednisolone dose should be reduced by approximately 25%, and the usual oral methylprednisolone dose should be reduced by approximately 50% when coadministered with EMEND (125 mg/80 mg regimen), to achieve exposures of methylprednisolone similar to those obtained when it is given without EMEND.

Chemotherapeutic agents: In clinical studies, EMEND (125 mg/80 mg regimen) was administered with the following chemotherapeutic agents metabolized primarily or in part by CYP3A4: etoposide, vinorelbine, docetaxel, paclitaxel, irinotecan, ifosfamide and cyclophosphamide. The doses of these agents were not adjusted to account for potential drug interactions. Caution and careful monitoring are advised in patients receiving these agents or other chemotherapy agents metabolized primarily by CYP3A4. Post-marketing events of neurotoxicity, a potential adverse reaction of ifosfamide, have been reported after aprepitant and ifosfamide coadministration (see PRECAUTIONS).

Docetaxel: In a separate pharmacokinetic study, EMEND (125 mg/80 mg regimen) did not influence the pharmacokinetics of docetaxel.

Vinorelbine: In a separate pharmacokinetic study, EMEND (125 mg/80 mg regimen) did not influence the pharmacokinetics of vinorelbine.

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 monitored in the 2-week period, particularly at 7 to 10 days following initiation of the 3-day regimen 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 µg 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 single dose of an oral contraceptive containing ethinyl estradiol and norethindrone was administered on Days 1 through 21 with EMEND, given as a 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 efficacy of hormonal contraceptives during and for 28 days after administration of EMEND may be reduced. 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 (125 mg/80 mg).

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.

An additional study was completed with intravenous administration of midazolam and EMEND. Intravenous midazolam 2 mg was given 1 hour after oral administration of a single dose of EMEND 125 mg. The plasma AUC of midazolam was increased by 1.5-fold. This effect was not considered clinically important.

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 cautiously; but concomitant administration of EMEND with moderate CYP3A4 inhibitors (e.g., diltiazem) does not result in clinically meaningful changes in plasma concentrations of aprepitant.

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. Concomitant administration of EMEND with St. John's wort is not recommended.

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 aprepitant 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 a 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.

Paroxetine: Coadministration of once daily doses of aprepitant, as a tablet formulation comparable to 85 mg or 170 mg of a 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.

XIII. SIDE EFFECTS

The overall safety of aprepitant was evaluated in approximately 6500 individuals.

PREVENTION OF CHEMOTHERAPY INDUCED NAUSEA AND VOMITING (CINV)

Highly Emetogenic Chemotherapy (HEC)

In 2 well-controlled clinical trials in patients receiving highly emetogenic cancer chemotherapy (HEC), 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 (aprepitant regimen) and was generally well tolerated. Most adverse experiences reported in these clinical studies were described as mild to moderate in intensity.

In Cycle 1, drug-related clinical adverse experiences were reported in approximately 17% of patients treated with the aprepitant regimen compared with approximately 13% of patients treated with standard therapy. Treatment was discontinued due to drug-related clinical adverse experiences in 0.6% of patients treated with the aprepitant regimen compared with 0.4% of patients treated with standard therapy.

The most common drug-related adverse experiences reported in patients treated with the aprepitant regimen and greater than standard therapy were: hiccups (4.6%), ALT increased (2.8%), dyspepsia (2.6%), constipation (2.4%), headache (2.0%), and decreased appetite (2.0%).

In an additional active-controlled clinical study in 1169 patients receiving aprepitant and HEC, the adverse experience profile was generally similar to that seen in the other HEC studies with aprepitant.

Moderately Emetogenic Chemotherapy (MEC)

In 2 well-controlled clinical trials in patients receiving moderately emetogenic cancer chemotherapy (MEC), 868 patients were treated with aprepitant during Cycle 1 of chemotherapy and 686 of these patients continued into extensions for up to 4 cycles of chemotherapy. In both studies, EMEND was given in combination with ondansetron and dexamethasone (aprepitant regimen) and was generally well tolerated. Most adverse experiences reported in these clinical studies were described as mild to moderate in intensity.

In the combined analysis of Cycle 1 data for these 2 studies, drug-related adverse experiences were reported in approximately 14% of patients treated with the aprepitant regimen compared with approximately 15% of patients treated with standard therapy. Treatment was discontinued due to drug-related clinical adverse experiences in 0.7% of

patients treated with the aprepitant regimen compared with 0.2% of patients treated with standard therapy.

The most common drug-related adverse experience reported at a greater incidence in patients treated with the aprepitant regimen than with standard therapy was fatigue (1.4%).

Highly and Moderately Emetogenic Chemotherapy

In a pooled analysis of the HEC and MEC studies, the following drug-related adverse experiences were reported in either HEC or MEC studies in patients treated with the aprepitant regimen and at a greater incidence than standard therapy:

[Common (≥1/100, <1/10) Uncommon (≥1/1000, <1/100), Rare (≥1/10,000, <1/1,000)]

Infections and Infestations:

Rare: candidiasis, staphylococcal infection.

Blood and the lymphatic system disorders:

Uncommon: anemia, febrile neutropenia.

Metabolism and nutrition disorders:

Common: decreased appetite.

Rare: polydipsia.

Psychiatric disorders:

Uncommon: anxiety.

Rare: disorientation, euphoric mood.

Nervous system disorders:

Uncommon: dizziness, somnolence.

Rare: cognitive disorder, lethargy, dysgeusia.

Eye disorders:

Rare: conjunctivitis.

Ear and labyrinth disorders:

Rare: tinnitus.

Cardiac disorders:

Uncommon: palpitations.

Rare: bradycardia, cardiovascular disorder.

Vascular disorders:

Uncommon: hot flush.

Respiratory, thoracic and mediastinal disorders:

Common: hiccups.

Rare: oropharyngeal pain, sneezing, cough, postnasal drip, throat irritation.

Gastrointestinal disorders:

Common: dyspepsia.

Uncommon: eructation, nausea, gastroesophageal reflux disease, vomiting, abdominal pain, dry mouth, flatulence.

Rare: feces hard, duodenal ulcer perforation, neutropenic colitis, stomatitis, abdominal distension.

Skin and subcutaneous tissue disorders:

Uncommon: rash, acne.

Rare: photosensitivity reaction, hyperhidrosis, seborrhea, skin lesion, rash pruritic.

Musculoskeletal and connective tissue disorders:

Rare: muscle spasms, muscular weakness.

Renal and urinary disorders:

Uncommon: dysuria.

Rare: pollakiuria.

General disorders and administration site conditions:

Common: fatigue.

Uncommon: asthenia, malaise.
Rare: edema, chest discomfort, gait disturbance.

Investigations:
Common: ALT increased.
Uncommon: AST increased, blood alkaline phosphatase increased.
Rare: urine output increased, red blood cells urine positive blood sodium decreased, weight decreased, glucose urine present, neutrophil count decreased.

The adverse experience profile in the Multiple-Cycle extension of HEC and MEC studies for up to 6 cycles of chemotherapy were generally similar to those observed in Cycle 1.

In another CINV study, Stevens-Johnson syndrome was reported as a serious adverse experience in a patient receiving aprepitant with cancer chemotherapy.

Other Studies
Single 40-mg doses of aprepitant have also been studied for the prevention of postoperative nausea and vomiting (PONV) in non-chemotherapy patients receiving general balanced anesthesia. In these studies, additional adverse reactions that were observed at a greater incidence than with the active comparator (ondansetron) included: ALT increased, abdominal pain upper, bowel sounds abnormal, dysarthria, dyspnoea, hypoaesthesia, insomnia, miosis, nausea, sensory disturbance, stomach discomfort, visual acuity reduced, wheezing.

In addition, two serious adverse experiences were reported in postoperative nausea and vomiting (PONV) clinical studies in patients taking a higher dose of aprepitant: one case of constipation, and one case of sub-ileus.

Angioedema and urticaria were reported as serious adverse experiences in a patient receiving aprepitant in a non-CINV/non-PONV study.

Post-Marketing Experience:

The following adverse reactions have been identified during post-marketing use of aprepitant. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to the drug.

Skin and subcutaneous tissue disorders: pruritus, rash, urticaria, rarely Stevens-Johnson syndrome/toxic epidermal necrolysis.
Immune system disorders: hypersensitivity reactions including anaphylactic reactions

XIV. OVERDOSAGE

No specific information is available on the treatment of overdosage 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.

XV. STORAGE

STORAGE CONDITION: Store at or below 30°C (86°F).

XVI. SHELF LIFE

Please refer to the expiry date on the outer carton.

XVII. AVAILABILITY

Packaging:

Tri-pack

EMEND is packaged in a pack containing 1 capsule of EMEND 125mg & 2 capsules of EMEND 80mg.

Appearance:

EMEND 80mg Capsule: White, opaque hard gelatin capsule with "461" and "80mg" printed radially in black ink.

EMEND 125mg Capsule: Opaque hard gelatin capsule with white body and pink cap, with "462" and "125mg" printed radially in black ink.

MANUFACTURED BY

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Ireland.

PACKED BY

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