HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use EMEND CAPSULES and EMEND FOR ORAL SUSPENSION safely and effectively. See full prescribing information for EMEND CAPSULES and EMEND FOR ORAL SUSPENSION.

EMEND (aprepitant) capsules, for oral use
EMEND (aprepitant) for oral suspension
Initial U.S. Approval: 2003

----------INDICATIONS AND USAGE----------

EMEND® is a substance P/neurokinin 1 (NK_1) receptor antagonist.

EMEND for oral suspension is indicated

- in combination with other antiemetic agents, in patients 6 months of age and older for prevention of:
  - acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including high-dose cisplatin (1.1)
  - nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC) (1.1)

EMEND capsules is indicated

- in combination with other antiemetic agents, in patients 12 years of age and older for prevention of:
  - acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including high-dose cisplatin (1.1)
  - nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC) (1.1)
- for prevention of postoperative nausea and vomiting (PONV) in adults (1.2)

Limitations of Use: (1.3)

- EMEND has not been studied for treatment of established nausea and vomiting.
- Chronic continuous administration of EMEND is not recommended.

---------- DOSAGE AND ADMINISTRATION ----------

Recommended Dosage for Prevention of Chemotherapy Induced Nausea and Vomiting (CINV) (2.1)

- EMEND capsules in adults and pediatric patients 12 years of age and older: is 125 mg on Day 1 and 80 mg on Days 2 and 3.
- EMEND for oral suspension in pediatric patients 6 months to less than 12 years of age or pediatric and adult patients unable to swallow capsules: see dosing recommendations in Table 3 in the Full Prescribing Information.
- Administer EMEND 1 hour prior to chemotherapy on Days 1, 2, and 3. If no chemotherapy is given on Days 2 and 3, administer EMEND in morning.
- See Full Prescribing Information for recommended dosages of concomitant dexamethasone and 5-HT_3 antagonist for HEC and MEC.

Recommended Dosage for PONV (2.2)

- Adults: 40 mg EMEND capsules within 3 hours prior to induction of anesthesia.

Preparation and Administration (2.3, 2.4)

- EMEND capsules and EMEND for oral suspension can be administered with or without food.
- Swallow EMEND capsules whole.
- EMEND for oral suspension should be prepared by healthcare provider. Once prepared, it may be administered either by a healthcare provider, patient, or caregiver.
- For details on preparation see Full Prescribing Information.

---------- DOSAGE FORMS AND STRENGTHS ----------

EMEND capsules: 40 mg; 80 mg; 125 mg (3)
EMEND for oral suspension: 125 mg (3)

----------CONTRAINDICATIONS----------

- Known hypersensitivity to any component of this drug. (4)
- Concurrent use with pimozide. (4)

---------- WARNINGS AND PRECAUTIONS ----------

- CYP3A4 Interactions: Aprepitant is a substrate, weak-to-moderate inhibitor and inducer of CYP3A4; See Full Prescribing Information for recommendations regarding contraindications, risk of adverse reactions, and dosage adjustments of EMEND and concomitant drugs. (4, 5.1, 7.1, 7.2)
- Warfarin (a CYP2C9 substrate): Risk of decreased INR of prothrombin time; monitor INR in 2-week period, particularly at 7 to 10 days, following initiation of EMEND. (5.2, 7.1)
- Hormonal Contraceptives: Efficacy of contraceptives may be reduced during administration of and for 28 days following the last dose of EMEND. Use effective alternative or back-up methods of contraception. (5.3, 7.1, 8.3)

---------- ADVERSE REACTIONS ----------

Most common adverse reactions are (6.1):
Prevention of Chemotherapy Induced Nausea and Vomiting (CINV)

- Adults (≥3%): fatigue, diarrhea, asthenia, dyspepsia, abdominal pain, hiccups, white blood cell count decreased, dehydration, and alanine aminotransferase increased.
- Pediatrics (≥3%): neutropenia, headache, diarrhea, decreased appetite, cough, fatigue, hemoglobin decreased, dizziness, and hiccups.

PONV

- Adults (≥3%): constipation and hypotension.

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

See Full Prescribing Information for a list of clinically significant drug interactions. (4, 5.1, 5.2, 5.3, 7.1, 7.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 01/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Prevention of Chemotherapy Induced Nausea and Vomiting (CINV)

EMEND® for oral suspension, in combination with other antiemetic agents, is indicated in patients 6 months of age and older for the prevention of:

- acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including high-dose cisplatin.
- nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC).

EMEND® capsules, in combination with other antiemetic agents, is indicated in patients 12 years of age and older for the prevention of:

- acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including high-dose cisplatin.
- nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC).

1.2 Prevention of Postoperative Nausea and Vomiting (PONV)

EMEND capsules are indicated in adults for the prevention of postoperative nausea and vomiting.

1.3 Limitations of Use

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

- Chronic continuous administration of EMEND is not recommended because it has not been studied, and because the drug interaction profile may change during chronic continuous use.

2 DOSAGE AND ADMINISTRATION

2.1 Prevention of Chemotherapy Induced Nausea and Vomiting (CINV)

Adults and Pediatric Patients 12 Years of Age and Older

The recommended oral dosage of EMEND capsules, dexamethasone, and a 5-HT_3 antagonist in adults and pediatric patients 12 years of age and older who can swallow oral capsules, for the prevention of nausea and vomiting associated with administration of HEC or MEC is shown in Table 1 or Table 2, respectively. For patients who cannot swallow oral capsules, EMEND for oral suspension can be used instead of EMEND capsules as shown in Table 3.

Table 1: Recommended Dosing for the Prevention of Nausea and Vomiting Associated with HEC

	Population	Day 1	Day 2	Day 3	Day 4
EMEND capsules*	Adults and Pediatric Patients 12 Years and Older	125 mg orally	80 mg orally	80 mg orally	none
Dexamethasone	Adults	12 mg orally	8 mg orally	8 mg orally	8 mg orally
	Pediatric Patients 12 Years and Older	If a corticosteroid, such as dexamethasone, is co-administered, administer 50% of the recommended corticosteroid dose on Days 1 through 4 *[see Clinical Studies (14.3)]*.†			
5-HT_3 antagonist	Adults and Pediatric Patients 12 Years and Older	See selected 5-HT_3 antagonist prescribing information for the recommended dosage	none	none	none

*Administer EMEND capsules 1 hour prior to chemotherapy treatment on Days 1, 2, and 3. If no chemotherapy is given on Days 2 and 3, administer EMEND capsules in the morning.
†Administer dexamethasone 30 minutes prior to chemotherapy treatment on Day 1 and in the morning on Days 2 through 4. A 50% dosage reduction of dexamethasone is recommended to account for a drug interaction with EMEND *[see Clinical Pharmacology (12.3)]*.

Table 2: Recommended Dosing for the Prevention of Nausea and Vomiting Associated with MEC

	Population	Day 1	Day 2	Day 3
EMEND capsules*	Adults and Pediatric Patients 12 Years and Older	125 mg orally	80 mg orally	80 mg orally
Dexamethasone	Adults	12 mg orally	none	none
	Pediatric Patients 12 Years and Older	If a corticosteroid, such as dexamethasone, is co-administered, administer 50% of the recommended corticosteroid dose on Days 1 through 4 *[see Clinical Studies (14.3)]*.†		
5-HT_3 antagonist	Adults and Pediatric Patients 12 Years and Older	See the selected 5-HT_3 antagonist prescribing information for recommended dosage	none	none

*Administer EMEND capsules 1 hour prior to chemotherapy treatment on Days 1, 2, and 3. If no chemotherapy is given on Days 2 and 3, administer EMEND capsules in the morning.
†Administer dexamethasone 30 minutes prior to chemotherapy treatment on Day 1. A 50% dosage reduction of dexamethasone is recommended to account for a drug interaction with EMEND *[see Clinical Pharmacology (12.3)]*.

Pediatric Patients 6 Months to less than 12 Years of Age or Pediatric and Adult Patients Unable to Swallow Capsules

The recommended dose of EMEND for oral suspension to be administered with a 5-HT_3 antagonist, with or without a corticosteroid, for the prevention of nausea and vomiting associated with administration

of HEC or MEC is specified in Table 3. Dosing of EMEND for oral suspension is based on weight, to a maximum of 125 mg on Day 1 and 80 mg on Days 2 and 3. Dosing in pediatric patients less than 6 kg is not recommended.

Table 3: Recommended Dosing in Pediatric Patients 6 Months to Less than 12 Years of Age or Pediatric and Adult Patients Unable to Swallow Capsules

	Population	Day 1	Day 2	Day 3	Day 4
EMEND for oral suspension*	Pediatric Patients 6 Months to Less than12 Years or Pediatric and Adult Patients Unable to Swallow Capsules	3 mg/kg orally Maximum dose 125 mg	2 mg/kg orally Maximum dose 80 mg	2 mg/kg orally Maximum dose 80 mg	none
Dexamethasone	Adults Unable to Swallow Capsules	See Table 1 or 2	See Table 1 or 2	See Table 1 or 2	See Table 1 or 2
	Pediatric Patients 6 Months to Less than12 Years or Pediatric Patients Unable to Swallow Capsules	If a corticosteroid, such as dexamethasone, is co-administered, administer 50% of the recommended corticosteroid dose on Days 1 through 4 *[see Clinical Studies (14.3)]*.†			
5-HT_3 antagonist	Pediatric Patients 6 Months to Less than12 Years or Pediatric and Adult Patients Unable to Swallow Capsules	See selected 5-HT_3 antagonist prescribing information for the recommended dosage	none	none	none

*After preparation, the final concentration of EMEND for oral suspension is 25 mg/mL *[see Dosage and Administration (2.3)]*. Administer EMEND for oral suspension 1 hour prior to chemotherapy treatment on Days 1, 2, and 3. If no chemotherapy is given on Days 2 and 3, administer EMEND for oral suspension in the morning.
†Administer dexamethasone 30 minutes prior to chemotherapy treatment on Day 1. A 50% dosage reduction of dexamethasone is recommended to account for a drug interaction with EMEND *[see Clinical Pharmacology (12.3)]*.

2.2 Prevention of Postoperative Nausea and Vomiting (PONV)

The recommended oral dosage of EMEND capsules in adults is 40 mg within 3 hours prior to induction of anesthesia.

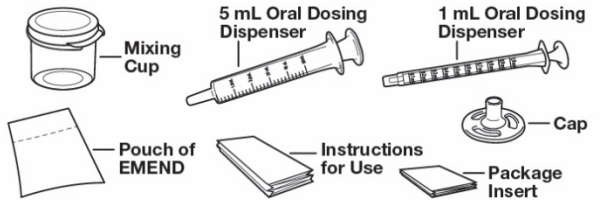
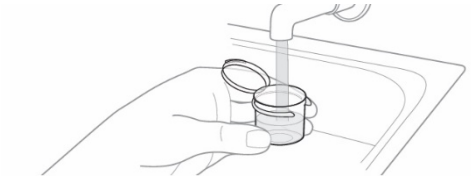
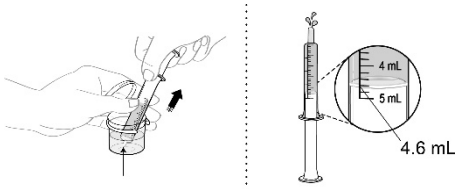
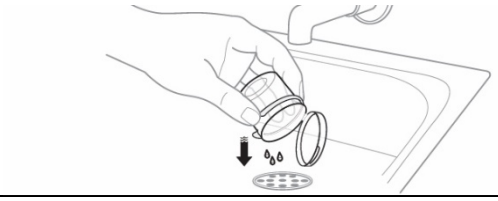
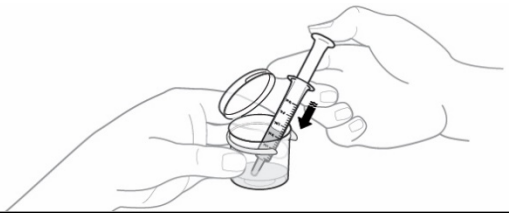
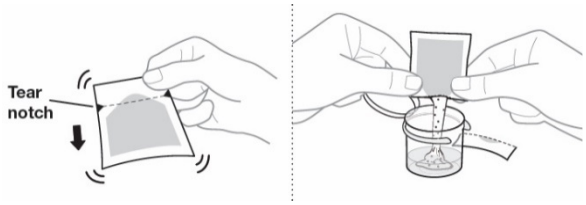
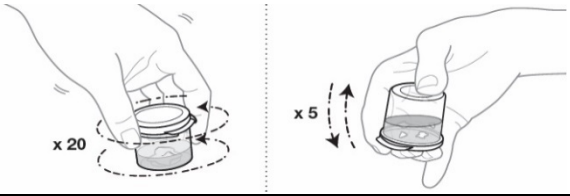
2.3 Preparation Instructions for EMEND for Oral Suspension -- for Healthcare Providers

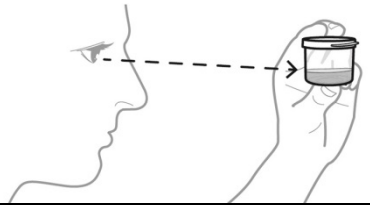
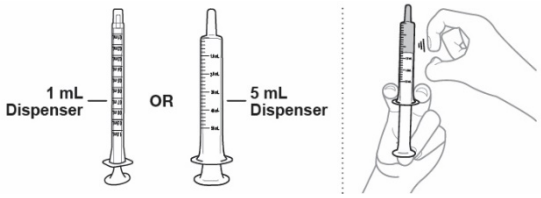
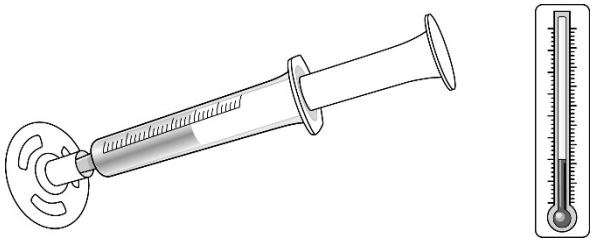
EMEND for oral suspension should be prepared by a healthcare provider.
Once prepared, it may be administered either by a healthcare provider, patient, or caregiver.

Before you prepare EMEND:

- Do not open the pouch of EMEND until ready to prepare the medicine.
- Store the pouch at room temperature [between 68°F-77°F (20°C-25°C)].

Table 4: Instructions for Healthcare Providers on How to Prepare EMEND for Oral Suspension

EMEND for oral suspension is packaged as a kit with one 1 mL oral dosing dispenser, one 5 mL oral dosing dispenser, one cap and one mixing cup.	
1. Fill the mixing cup with room temperature drinking water.	
2. Fill the 5 mL oral dosing dispenser with 4.6 mL of water from the mixing cup. **Make sure no air is in the dispenser - if air is present, remove.**	
3. Discard all the unused water remaining in the mixing cup.	
4. Add the 4.6 mL of water from the dispenser back into the mixing cup.	
5. Each pouch of EMEND for oral suspension contains 125 mg of aprepitant which is to be suspended in 4.6 mL of water giving a final concentration of 25 mg/mL. Hold the EMEND for oral suspension pouch upright and shake the contents to the bottom before opening the pouch. 6. Pour the entire contents of the pouch into the 4.6 mL of water in the mixing cup and snap the lid shut.	
7. Mix the EMEND suspension gently by swirling 20 times; then gently invert the mixing cup 5 times. To prevent foaming, do not shake the mixing cup. The mixture will be cloudy pink to light pink.	

8. Check the EMEND mixture for any clumps or foaming: • If any clumps are present, repeat Step 7 until there are no clumps. • If there is any foam, wait for the foam to disappear before going on to Step 9.	
9. Fill the dispenser with the prescribed dose shown above in Table 3. • Choose the dispenser based on dose: o Use 1 mL dispenser if dose is 1 mL or less. o Use 5 mL dispenser if dose is more than 1 mL. • Fill the dispenser with the prescribed dose from the cup. o If the dose is less than 1 mL round to the nearest 0.1 mL. o If the dose is more than 1 mL round to the nearest 0.2 mL. • It is common to have medicine leftover in the cup. **Make sure no air is in the dispenser - if air is present, remove.** **Make sure the dispenser contains the prescribed dose.**	
10. Place the cap on the dispenser until it clicks. 11. If the dose is not administered immediately after measuring, store filled oral dosing dispenser(s) in the refrigerator [between 36°F-46°F (2°C-8°C)] for up to 72 hours prior to use. When dispensing dose(s) to the patient or caregiver, instruct them to refrigerate the oral dosing dispenser(s) until they are ready to administer the dose. 12. When ready to use, the mixture can be kept at room temperature [between 68°F-77°F (20°C-25°C)] for up to 3 hours.	
13. Discard the mixing cup along with any remaining suspension.	

2.4 Administration Instructions

EMEND capsules and EMEND for oral suspension can be administered with or without food.

<u>EMEND capsules</u>

- Swallow capsules whole.

EMEND for oral suspension

- The dose will be prepared by the healthcare provider and dispensed to the patient or caregiver in an oral dispenser.
- Keep the dispenser in the refrigerator until administered to the patient. The dose can be stored at room temperature for up to 3 hours before use.
- When ready to use, take the cap off the dispenser, place the dispenser in the patient's mouth along the inner cheek on either the right or left side. Slowly dispense the medicine.
- The dose must be used within 72 hours of preparation.
- Discard any doses remaining after 72 hours.

3 DOSAGE FORMS AND STRENGTHS

EMEND capsules:

- 40 mg: white body and mustard yellow cap with "464" and "40 mg" printed radially in black ink on the body.
- 80 mg: white body and cap with "461" and "80 mg" printed radially in black ink on the body.
- 125 mg: white body and pink cap with "462" and "125 mg" printed radially in black ink on the body.

EMEND for oral suspension:

- 125 mg as a pink to light pink powder in a single-use pouch with one 1 mL oral dosing dispenser, one 5 mL oral dosing dispenser, one cap and mixing cup.

4 CONTRAINDICATIONS

EMEND is contraindicated in patients:

- who are hypersensitive to any component of the product. Hypersensitivity reactions including anaphylactic reactions have been reported *[see Adverse Reactions (6.2)]*.
- taking pimozide. Inhibition of CYP3A4 by aprepitant could result in elevated plasma concentrations of this drug which is a CYP3A4 substrate, potentially causing serious or life-threatening reactions, such as QT prolongation, a known adverse reaction of pimozide *[see Warnings and Precautions (5.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Clinically Significant CYP3A4 Drug Interactions

Aprepitant is a substrate, a weak-to-moderate (dose-dependent) inhibitor, and an inducer of CYP3A4.

- Use of EMEND with other drugs that are CYP3A4 substrates, may result in increased plasma concentration of the concomitant drug.
  - Use of pimozide with EMEND is contraindicated due to the risk of significantly increased plasma concentrations of pimozide, potentially resulting in prolongation of the QT interval, a known adverse reaction of pimozide *[see Contraindications (4)].*
- Use of EMEND with strong or moderate CYP3A4 inhibitors (e.g., ketoconazole, diltiazem) may increase plasma concentrations of aprepitant and result in an increased risk of adverse reactions related to EMEND.
- Use of EMEND with strong CYP3A4 inducers (e.g., rifampin) may result in a reduction in aprepitant plasma concentrations and decreased efficacy of EMEND.

See Table 10 and Table 11 for a listing of potentially significant drug interactions *[see Drug Interactions (7.1, 7.2)].*

5.2 Decrease in INR with Concomitant Warfarin

Coadministration of EMEND with warfarin, a CYP2C9 substrate, may result in a clinically significant decrease in International Normalized Ratio (INR) of prothrombin time *[see Clinical Pharmacology (12.3)]*. Monitor the INR in patients on chronic warfarin therapy in the 2-week period, particularly at 7 to 10 days, following initiation of the 3-day regimen of EMEND with each chemotherapy cycle, or following

administration of a single 40-mg dose of EMEND for the prevention of postoperative nausea and vomiting *[see Drug Interactions (7.1)]*.

5.3 Risk of Reduced Efficacy of Hormonal Contraceptives

Upon coadministration with EMEND, the efficacy of hormonal contraceptives may be reduced during administration of and for 28 days following the last dose of EMEND *[see Clinical Pharmacology (12.3)]*. Advise patients to use effective alternative or back-up methods of contraception during treatment with EMEND and for 1 month following the last dose of EMEND *[see Drug Interactions (7.1), Use in Specific Populations (8.3)]*.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The overall safety of EMEND was evaluated in approximately 6800 individuals.

Adverse Reactions in Adults in the Prevention of Nausea and Vomiting Associated with HEC and MEC

In 2 active-controlled, double-blind clinical trials in patients receiving highly emetogenic chemotherapy (HEC) (Studies 1 and 2), EMEND in combination with ondansetron and dexamethasone (EMEND regimen) was compared to ondansetron and dexamethasone alone (standard therapy) *[see Clinical Studies (14.1)]*.

In 2 active-controlled clinical trials in patients receiving moderately emetogenic chemotherapy (MEC) (Studies 3 and 4), EMEND in combination with ondansetron and dexamethasone (EMEND regimen) was compared to ondansetron and dexamethasone alone (standard therapy) *[see Clinical Studies (14.2)].* The most common adverse reaction reported in patients who received MEC in pooled Studies 3 and 4 was dyspepsia (6% versus 4%).

Across these 4 studies there were 1412 patients treated with the EMEND regimen during Cycle 1 of chemotherapy and 1099 of these patients continued into the Multiple-Cycle extension for up to 6 cycles of chemotherapy. The most common adverse reactions reported in patients who received HEC and MEC in pooled Studies 1, 2, 3 and 4 are listed in Table 5.

Table 5: Most Common Adverse Reactions in Patients Receiving HEC and MEC from a Pooled Analysis of HEC and MEC Studies*

	EMEND, ondansetron, and dexamethasone† (N=1412)	**Ondansetron and dexamethasone‡ (N=1396)**
fatigue	13%	12%
diarrhea	9%	8%
asthenia	7%	6%
dyspepsia	7%	5%
abdominal pain	6%	5%
hiccups	5%	3%
white blood cell count decreased	4%	3%
dehydration	3%	2%
alanine aminotransferase increased	3%	2%

*Reported in ≥ 3% of patients treated with the EMEND regimen and at a greater incidence than standard therapy.
†EMEND regimen
‡Standard therapy

In a pooled analysis of the HEC and MEC studies, less common adverse reactions reported in patients treated with the EMEND regimen are listed in Table 6.

Table 6: Less Common Adverse Reactions in EMEND-Treated Patients from a Pooled Analysis of HEC and MEC Studies*

Infection and Infestations	oral candidiasis, pharyngitis
Blood and the Lymphatic System Disorders	anemia, febrile neutropenia, neutropenia, thrombocytopenia
Metabolism and Nutrition Disorders	decreased appetite, hypokalemia
Psychiatric Disorders	anxiety
Nervous System Disorders	dizziness, dysgeusia, peripheral neuropathy
Cardiac Disorders	palpitations
Vascular Disorders	flushing, hot flush
Respiratory, Thoracic and Mediastinal Disorders	cough, dyspnea, oropharyngeal pain
Gastrointestinal Disorders	dry mouth, eructation, flatulence, gastritis, gastroesophageal reflux disease, nausea, vomiting
Skin and Subcutaneous Tissue Disorders	alopecia, hyperhidrosis, rash
Musculoskeletal and Connective Tissue Disorders	musculoskeletal pain
General Disorders and Administration Site Condition	edema peripheral, malaise
Investigations	aspartate aminotransferase increased, blood alkaline phosphatase increased, blood sodium decreased, blood urea increased, proteinuria, weight decreased

*Reported in > 0.5% of patients treated with the EMEND regimen, at a greater incidence than standard therapy and not previously described in Table 5.

In an additional active-controlled clinical study in 1169 patients receiving EMEND and HEC, the adverse reactions were generally similar to that seen in the other HEC studies with EMEND.

In another CINV study, Stevens-Johnson syndrome was reported as a serious adverse reaction in a patient receiving the EMEND regimen with cancer chemotherapy.

Adverse reactions in the Multiple-Cycle extensions of HEC and MEC studies for up to 6 cycles of chemotherapy were generally similar to that observed in Cycle 1.

Adverse Reactions in Pediatric Patients 6 Months to 17 Years of Age in the Prevention of Nausea and Vomiting Associated with HEC or MEC

In a pooled analysis of 2 active-controlled clinical trials in pediatric patients aged 6 months to 17 years who received highly or moderately emetogenic cancer chemotherapy (Study 5 and a safety study, Study 6), EMEND in combination with ondansetron with or without dexamethasone (EMEND regimen) was compared to ondansetron with or without dexamethasone (control regimen).

There were 184 patients treated with the EMEND regimen during Cycle 1 and 215 patients received open-label EMEND for up to 9 additional cycles of chemotherapy.

In Cycle 1, the most common adverse reactions reported in pediatric patients treated with the EMEND regimen in pooled Studies 5 and 6 are listed in Table 7.

Table 7: Most Common Adverse Reactions in EMEND-Treated Pediatric Patients in HEC and MEC Pooled Studies 5 and 6*

	EMEND and ondansetron† (N=184)	Ondansetron‡ (N=168)
neutropenia	13%	11%
headache	9%	5%
diarrhea	6%	5%
decreased appetite	5%	4%
cough	5%	3%
fatigue	5%	2%
hemoglobin decreased	5%	4%
dizziness	5%	1%
hiccups	4%	1%

*Reported in ≥3% of patients treated with the EMEND regimen and at a greater incidence than control regimen.
†EMEND regimen
‡Control regimen

Forty-nine patients were treated with ifosfamide chemotherapy in each arm. Two of the patients treated with ifosfamide in the aprepitant arm developed behavioral changes (agitation = 1; abnormal behavior = 1), whereas no patient treated with ifosfamide in the control arm developed behavioral changes. Aprepitant has the potential for increasing ifosfamide-mediated neurotoxicity through induction of CYP3A4 *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3)]*.

Adverse Reactions in Adult Patients in the Prevention of PONV

In 2 active-controlled, double-blind clinical studies in patients receiving general anesthesia (Studies 7 and 8), 40-mg oral EMEND was compared to 4-mg intravenous ondansetron *[see Clinical Studies (14.4)].*

There were 564 patients treated with EMEND and 538 patients treated with ondansetron.

The most common adverse reactions reported in patients treated with EMEND for PONV in pooled Studies 7 and 8 are listed in Table 8.

Table 8: Most Common Adverse Reactions in EMEND-Treated Patients in a Pooled Analysis of PONV Studies*

	EMEND 40 mg (N = 564)	Ondansetron (N = 538)
constipation	9%	8%
hypotension	6%	5%

*Reported in ≥ 3% of patients treated with the EMEND 40 mg and at a greater incidence than ondansetron.

In a pooled analysis of PONV studies, less common adverse reactions reported in patients treated with EMEND are listed in Table 9.

Table 9: Less Common Adverse Reactions in EMEND-Treated Patients in a Pooled Analysis of PONV Studies*

Infections and Infestations	postoperative infection
Metabolism and Nutrition Disorders	hypokalemia, hypovolemia
Nervous System Disorders	dizziness, hypoesthesia, syncope
Cardiac Disorders	bradycardia
Vascular Disorders	hematoma
Respiratory, Thoracic and Mediastinal Disorders	dyspnea, hypoxia, respiratory depression
Gastrointestinal Disorders	abdominal pain, dry mouth, dyspepsia
Skin and Subcutaneous Tissue Disorders	urticaria
General Disorders and Administration Site Conditions	hypothermia
Investigations	blood albumin decreased, bilirubin increased, blood glucose increased, blood potassium decreased
Injury, Poisoning and Procedural Complications	operative hemorrhage, wound dehiscence

*Reported in > 0.5% of patients treated with EMEND and at a greater incidence than ondansetron

In addition, two serious adverse reactions were reported in PONV clinical studies in patients taking a higher than recommended dose of EMEND: one case of constipation, and one case of sub-ileus.

Other Studies

Angioedema and urticaria were reported as serious adverse reactions in a patient receiving EMEND in a non-CINV/non-PONV study (EMEND is only approved in the CINV and PONV populations).

6.2 Postmarketing Experience

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

Skin and subcutaneous tissue disorders: pruritus, rash, urticaria, Stevens-Johnson syndrome/toxic epidermal necrolysis.

Immune system disorders: hypersensitivity reactions including anaphylactic reactions *[see Contraindications (4)]*.

Nervous system disorders: ifosfamide-induced neurotoxicity reported after EMEND and ifosfamide coadministration.

7 DRUG INTERACTIONS

7.1 Effect of Aprepitant on the Pharmacokinetics of Other Drugs

Aprepitant is a substrate, a weak-to-moderate (dose-dependent) inhibitor, and an inducer of CYP3A4. Aprepitant is also an inducer of CYP2C9 *[see Clinical Pharmacology (12.3)]*.

Aprepitant acts as a moderate inhibitor of CYP3A4 when administered as a 3-day regimen (125-mg/80-mg/80-mg) and can increase plasma concentrations of concomitant drugs that are substrates for CYP3A4. Aprepitant acts as a weak inhibitor when administered as a single 40-mg dose and has not been shown to alter the plasma concentrations of concomitant drugs that are primarily metabolized through CYP3A4. Some substrates of CYP3A4 are contraindicated with EMEND *[see Contraindications (4)]*. Dosage adjustment of some CYP3A4 and CYP2C9 substrates may be warranted, as shown in Table 10.

Table 10: Effects of Aprepitant on the Pharmacokinetics of Other Drugs

CYP3A4 Substrates	
Pimozide	
Clinical Impact	Increased pimozide exposure
Intervention	EMEND is contraindicated *[see Contraindications (4)]*.

Benzodiazepines	
Clinical Impact	Increased exposure to midazolam or other benzodiazepines metabolized via CYP3A4 (alprazolam, triazolam) may increase the risk of adverse reactions *[see Clinical Pharmacology (12.3)].*
Intervention	3-day EMEND regimen • Monitor for benzodiazepine-related adverse reactions. • Depending on the clinical situation (e.g., elderly patients) and degree of monitoring available, reduce the dose of intravenous midazolam Single 40 mg dose of EMEND • No dosage adjustment of the benzodiazepine needed
Dexamethasone	
Clinical Impact	Increased dexamethasone exposure *[see Clinical Pharmacology (12.3)].*
Intervention	3-day EMEND regimen • Reduce the dose of oral dexamethasone by approximately 50% *[see Dosage and Administration (2.1)].* Single 40 mg dose of EMEND • No dosage adjustment of oral dexamethasone needed
Methylprednisolone	
Clinical Impact	Increased methylprednisolone exposure *[see Clinical Pharmacology (12.3)].*
Intervention	3-day EMEND regimen • Reduce the dose of intravenous methylprednisolone by approximately 25% • Reduce the dose of oral methylprednisolone by approximately 50% Single 40 mg dose of EMEND • No dosage adjustment of methylprednisolone needed
Chemotherapeutic agents that are metabolized by CYP3A4	
Clinical Impact	Increased exposure of the chemotherapeutic agent may increase the risk of adverse reactions *[see Clinical Pharmacology (12.3)]*.
Intervention	Vinblastine, vincristine, or ifosfamide or other chemotherapeutic agents • Monitor for chemotherapeutic-related adverse reactions. Etoposide, vinorelbine, paclitaxel, and docetaxel • No dosage adjustment needed.
Hormonal Contraceptives	
Clinical Impact	Decreased hormonal exposure during administration of and for 28 days after administration of the last dose of EMEND *[see Warnings and Precautions (5.3), Use in Specific Populations (8.3), Clinical Pharmacology (12.3)]*.
Intervention	Effective alternative or back-up methods of contraception (such as condoms and spermicides) should be used during treatment with EMEND and for 1 month following the last dose of EMEND.
Examples	birth control pills, skin patches, implants, and certain IUDs
CYP2C9 Substrates	
Warfarin	
Clinical Impact	Decreased warfarin exposure and decreased prothrombin time (INR) *[see Warnings and Precautions (5.2), Clinical Pharmacology (12.3)]*.
Intervention	In patients on chronic warfarin therapy, monitor the prothrombin time (INR) in the 2-week period, particularly at 7 to 10 days, following initiation of the 3-day EMEND regimen with each chemotherapy cycle, or following administration of a single 40-mg dose of EMEND.
Other	
5-HT_3 Antagonists	

Clinical Impact	No change in the exposure of the 5-HT_3 antagonist *[see Clinical Pharmacology (12.3)]*.
Intervention	No dosage adjustment needed
Examples	ondansetron, granisetron, dolasetron

7.2 Effect of Other Drugs on the Pharmacokinetics of Aprepitant

Aprepitant is a CYP3A4 substrate *[see Clinical Pharmacology (12.3)]*. Co-administration of EMEND with drugs that are inhibitors or inducers of CYP3A4 may result in increased or decreased plasma concentrations of aprepitant, respectively, as shown in Table 11.

Table 11: Effects of Other Drugs on Pharmacokinetics of Aprepitant

Moderate to Strong CYP3A4 Inhibitors	
Clinical Impact	Significantly increased exposure of aprepitant may increase the risk of adverse reactions associated with EMEND *[see Adverse Reactions (6.1) and Clinical Pharmacology (12.3)]*.
Intervention	Avoid concomitant use of EMEND
Examples	Moderate inhibitor: diltiazem Strong inhibitors: ketoconazole, itraconazole, nefazodone, troleandomycin, clarithromycin, ritonavir, nelfinavir
Strong CYP3A4 Inducers	
Clinical Impact	Substantially decreased exposure of aprepitant in patients chronically taking a strong CYP3A4 inducer may decrease the efficacy of EMEND *[see Clinical Pharmacology (12.3)]*.
Intervention	Avoid concomitant use of EMEND
Examples	rifampin, carbamazepine, phenytoin

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are insufficient data on use of EMEND in pregnant women to inform a drug associated risk. In animal reproduction studies, no adverse developmental effects were observed in rats or rabbits exposed during the period of organogenesis to systemic drug levels (AUC) approximately 1.5 times the adult human exposure at the 125-mg/80-mg/80-mg EMEND regimen *[see Data]*.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

In embryofetal development studies in rats and rabbits, aprepitant was administered during the period of organogenesis at oral doses up to 1000 mg/kg twice daily in rats and up to the maximum tolerated dose of 25 mg/kg/day in rabbits. No embryofetal lethality or malformations were observed at any dose level in either species. The exposures (AUC) in pregnant rats at 1000 mg/kg twice daily and in pregnant rabbits at 125 mg/kg/day were approximately 1.5 times the adult exposure at the 125-mg/80-mg/80-mg EMEND regimen. Aprepitant crosses the placenta in rats and rabbits.

8.2 Lactation

Risk Summary

Lactation studies have not been conducted to assess the presence of aprepitant in human milk, the effects on the breastfed infant, or the effects on milk production. Aprepitant is present in rat milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical

need for EMEND and any potential adverse effects on the breastfed infant from EMEND or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Contraception

Upon administration of EMEND, the efficacy of hormonal contraceptives may be reduced. Advise females of reproductive potential using hormonal contraceptives to use an effective alternative or back-up non-hormonal contraceptive (such as condoms and spermicides) during treatment with EMEND and for 1 month following the last dose *[see Drug Interactions (7.1), Clinical Pharmacology (12.3)]*.

8.4 Pediatric Use

Prevention of Nausea and Vomiting Associated with HEC or MEC

The safety and effectiveness of EMEND for oral suspension have been established in pediatric patients 6 months of age and older and EMEND capsules in pediatric patients 12 years of age and older for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of HEC, including high-dose cisplatin, and MEC. Use of EMEND in these age groups is supported by evidence from 302 pediatric patients in a randomized, double-blind, active comparator controlled clinical study (n = 207 patients aged 6 months to less than 12 years, n = 95 patients aged 12 through 17 years). EMEND was studied in combination with ondansetron with or without dexamethasone (at the discretion of the physician) *[see Clinical Studies (14.3)]*. Adverse reactions were similar to those reported in adult patients *[see Adverse Reactions (6.1)]*.

The safety and effectiveness of EMEND for the prevention of nausea and vomiting associated with HEC or MEC have not been established in patients less than 6 months.

Prevention of Postoperative Nausea and Vomiting (PONV)

The safety and effectiveness of EMEND have not been established for the prevention of postoperative nausea and vomiting in pediatric patients.

Juvenile Animal Study

A study was conducted in young rats to evaluate the effects of aprepitant on growth and on neurobehavioral and sexual development. Rats were treated at oral 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 pediatric human dose and exposure in female rats equivalent to the pediatric human exposure) from the early postnatal period (Postnatal Day 10) through Postnatal Day 58. Slight changes in the onset of sexual maturation were observed in female and male rats; however, there were no effects on mating, fertility, embryonic-fetal survival, or histomorphology of the reproductive organs. There were no effects in neurobehavioral tests of sensory function, motor function, and learning and memory.

8.5 Geriatric Use

Of the 544 adult cancer patients treated with EMEND in CINV clinical studies, 31% were aged 65 and over, while 5% were aged 75 and over. Of the 1120 adult cancer patients treated with EMEND in PONV clinical studies, 7% were aged 65 and over, while 2% were aged 75 and over. Other reported clinical experience with EMEND has not identified differences in responses between elderly and younger patients. In general, use caution when dosing elderly patients as they have a greater frequency of decreased hepatic, renal or cardiac function and concomitant disease or other drug therapy *[see Clinical Pharmacology (12.3)]*.

8.6 Patients with Renal Impairment

The pharmacokinetics of aprepitant in patients with severe renal impairment and those with end stage renal disease (ESRD) requiring hemodialysis were similar to those of healthy subjects with normal renal function. No dosage adjustment is necessary for patients with any degree of renal impairment or for patients with ESRD undergoing hemodialysis.

8.7 Patients with Hepatic Impairment

The pharmacokinetics of aprepitant in patients with mild and moderate hepatic impairment were similar to those of healthy subjects with normal hepatic function. No dosage adjustment is necessary for patients with mild to moderate hepatic impairment (Child-Pugh score 5 to 9). There are no clinical or pharmacokinetic data in patients with severe hepatic impairment (Child-Pugh score greater than 9). Therefore, additional monitoring for adverse reactions in these patients may be warranted when EMEND is administered *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

No specific information is available on the treatment of overdosage.

Drowsiness and headache were reported in one patient who ingested 1440 mg of EMEND (approximately 11 times the maximum recommended single dose).

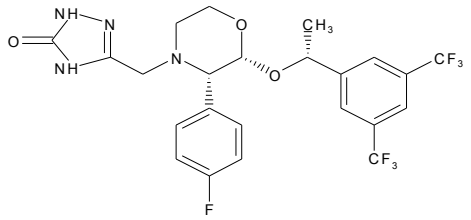
In the event of overdose, EMEND should be discontinued and general supportive treatment and monitoring should be provided. Because of the antiemetic activity of EMEND, drug-induced emesis may not be effective in cases of EMEND overdosage.

Aprepitant is not removed by hemodialysis.

11 DESCRIPTION

EMEND capsules contain the active ingredient, aprepitant. Aprepitant is a substance P/neurokinin 1 (NK_1) receptor antagonist, an antiemetic agent, 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 $C_{23}H_{21}F_7N_4O_3$, 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 40 mg, 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 40-mg capsule shell also contains yellow ferric oxide, and the 125-mg capsule also contains red ferric oxide and yellow ferric oxide.

Each pouch of EMEND for oral suspension 125 mg contains 125 mg of aprepitant and the following inactive ingredients: sucrose, lactose, hydroxypropyl cellulose, sodium lauryl sulfate, red iron oxide, and sodium stearyl fumarate.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Aprepitant is a selective high-affinity antagonist of human substance P/neurokinin 1 (NK_1) receptors. Aprepitant has little or no affinity for serotonin (5-HT_3), dopamine, and corticosteroid receptors, the targets of existing therapies for chemotherapy-induced nausea and vomiting (CINV) and postoperative nausea and vomiting (PONV).

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_1 receptors. Animal and human studies show that aprepitant augments the antiemetic

activity of the 5-HT_3-receptor antagonist ondansetron and the corticosteroid dexamethasone and inhibits both the acute and delayed phases of cisplatin-induced emesis.

12.2 Pharmacodynamics

NK_1 Receptor Occupancy

In two single-blind, multiple-dose, randomized, and placebo-controlled studies, healthy young men received oral EMEND doses of 10 mg (N=2), 30 mg (N=3), 100 mg (N=3) or 300 mg (N=5) once daily (0.08, 0.24, 0.8, and 2.4 times the maximum recommended single dose, respectively) for 14 days with 2 or 3 subjects on placebo. Both plasma aprepitant concentration and NK_1 receptor occupancy in the corpus striatum by positron emission tomography were evaluated, at predose and 24 hours after the last dose. At aprepitant plasma concentrations of ~10 ng/mL and ~100 ng/mL, the NK_1 receptor occupancies were ~50% and ~90%, respectively. The oral EMEND regimen for CINV produced mean trough plasma aprepitant concentrations greater than 500 ng/mL in adults, which would be expected to, based on the fitted curve with the Hill equation, result in greater than 95% brain NK_1 receptor occupancy. However, the receptor occupancy for either CINV or PONV dosing regimen has not been determined. In addition, the relationship between NK_1 receptor occupancy and the clinical efficacy of EMEND has not been established.

Cardiac Electrophysiology

In a randomized, double-blind, positive-controlled, thorough QTc study, a single 200-mg dose of fosaprepitant had no effect on the QTc interval. Maximum aprepitant concentrations after a single 200-mg dose of fosaprepitant were 4- and 9-fold higher than that achieved with oral EMEND 125 mg and 40 mg, respectively. QT prolongation with the oral EMEND dosing regimens for CINV and PONV is not expected.

12.3 Pharmacokinetics

Absorption

Following oral administration of a single 40-mg dose of EMEND in the fasted state, mean area under the plasma concentration-time curve ($AUC_{0-\infty}$) was 7.8 mcg•hr/mL and mean peak plasma concentration (C_{max}) was 0.7 mcg/mL, occurring at approximately 3 hours postdose (T_{max}). The absolute bioavailability at the 40-mg dose has not been determined.

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 19.6 mcg•hr/mL and 21.2 mcg•hr/mL on Day 1 and Day 3, respectively. The C_{max} of 1.6 mcg/mL and 1.4 mcg/mL were reached in approximately 4 hours (T_{max}) on Day 1 and Day 3, respectively. At the dose range of 80 to 125 mg, the mean absolute oral bioavailability of EMEND is approximately 60 to 65%. Oral administration of the capsule with a standard high-fat breakfast had no clinically meaningful effect on the bioavailability of aprepitant.

The pharmacokinetics of aprepitant were 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.

Distribution

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

Aprepitant crosses the blood brain barrier in humans *[see Clinical Pharmacology (12.1)]*.

Elimination

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 (2.4 times the maximum recommended dose), 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 intravenous 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.

Specific Populations

Age: Geriatric Population

Following oral administration of a single 125-mg dose of EMEND on Day 1 and 80 mg once daily on Days 2 through 5 (2 additional days of dosing compared to the recommended duration), the $AUC_{0\text{-}24hr}$ of aprepitant was 21% higher on Day 1 and 36% higher on Day 5 in elderly (65 years and older) 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 *[see Use in Specific Populations (8.5)]*.

Age: Pediatric Population

As part of a 3-day regimen, dosing of aprepitant capsules (125-mg/80-mg/80-mg) in 18 pediatric patients (aged 12 through 17 years) achieved a mean $AUC_{0\text{-}24hr}$ of 17 mcg•hr/mL on Day 1 with mean peak plasma concentration (C_{max}) at 1.3 mcg/mL occurring at approximately 4 hours. The mean concentrations at the end of Day 2 (N=8) and Day 3 (N=16) were both at 0.6 mcg/mL

As part of a 3-day regimen, weight-based dosing of aprepitant powder for oral suspension (3-mg/kg;2-mg/kg;2-mg/kg) in 18 pediatric patients aged 6 months to less than 12 years achieved a mean $AUC_{0\text{-}24hr}$ of 20.9 mcg•hr/mL on Day 1 with mean peak plasma concentration (C_{max}) at 1.8 mcg/mL (N=19), occurring at approximately 6 hours. The mean concentrations at the end of Day 2 (N=18) and Day 3 (N=19) were 0.4 mcg/mL and 0.5 mcg/mL, respectively *[see Dosage and Administration (2.1)]*.

A population pharmacokinetic analysis of aprepitant in pediatric patients (aged 6 months through 17 years) suggests that sex and race have no clinically meaningful effect on the pharmacokinetics of aprepitant.

Sex

Following oral administration of a single dose of EMEND ranging from 40 mg to 375 mg (3 times the maximum recommended dose), the $AUC_{0\text{-}24hr}$ and C_{max} are 9% and 17% higher in females as compared with males. The half-life of aprepitant is approximately 25% lower in females as compared with males and T_{max} occurs at approximately the same time. These differences are not considered clinically meaningful.

Race/Ethnicity

Following oral administration of a single dose of EMEND ranging from 40 mg to 375 mg (3 times the maximum recommended dose), the $AUC_{0\text{-}24hr}$ and C_{max} are approximately 27% and 19% higher in Hispanics as compared with Caucasians. The $AUC_{0\text{-}24hr}$ and C_{max} were 74% and 47% higher in Asians as compared to Caucasians. There was no difference in $AUC_{0\text{-}24hr}$ or C_{max} between Caucasians and Blacks. These differences are not considered clinically meaningful.

Renal Impairment

A single 240-mg dose of EMEND (approximately 1.9 times the maximum recommended dose) was administered to patients with severe renal impairment (creatinine clearance less than 30 mL/min/1.73 m^2 as measured by 24-hour urinary creatinine clearance) and to patients with end stage renal disease (ESRD) requiring hemodialysis.

In patients with severe renal impairment, the $AUC_{0-\infty}$ of total aprepitant (unbound and protein bound) decreased by 21% and C_{max} decreased by 32%, relative to healthy subjects (creatinine clearance greater than 80 mL/min estimated by Cockcroft-Gault method). 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 impairment 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 *[see Use in Specific Populations (8.6)]*.

Hepatic Impairment

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 impairment (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 impairment (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. There are no clinical or pharmacokinetic data in patients with severe hepatic impairment (Child-Pugh score greater than 9) *[see Use in Specific Populations (8.7)]*.

Body Mass Index (BMI)

For every 5 kg/m^2 increase in BMI, AUC_{0-24hr} and C_{max} of aprepitant decrease by 9% and 10%. BMI of subjects in the analysis ranged from 18 kg/m^2 to 36 kg/m^2. This change is not considered clinically meaningful.

Drug Interactions Studies

Aprepitant is a substrate, a weak-to-moderate (dose-dependent) inhibitor, and an inducer of CYP3A4. Aprepitant is also an inducer of CYP2C9. Aprepitant is unlikely to interact with drugs that are substrates for the P-glycoprotein transporter.

Effects of Aprepitant on the Pharmacokinetics of Other Drugs

CYP3A4 substrates (i.e., midazolam): Interactions between EMEND and coadministered midazolam are listed in Table 12 (increase is indicated as "↑", decrease as "↓", no change as "↔").

Table 12: Pharmacokinetic Interaction Data for EMEND and Coadministered Midazolam

Dosage of EMEND	Dosage of Midazolam	Observed Drug Interactions
EMEND 125 mg on Day 1 and 80 mg on Days 2 to 5	oral 2 mg single dose on Days 1 and 5	midazolam AUC ↑ 2.3-fold on Day 1 and ↑ 3.3-fold on Day 5 *[see Drug Interactions (7.1)]*
EMEND 125 mg on Day 1 and 80 mg on Days 2 and 3	intravenous 2 mg prior to 3-day regimen of EMEND and on Days 4, 8 and 15	midazolam AUC ↑ 25% on Day 4, AUC ↓ 19% on Day 8 and AUC ↓ 4% on Day 15
EMEND 125 mg	intravenous 2 mg given 1 hour after EMEND	midazolam AUC ↑ 1.5-fold
EMEND 40 mg	oral 2 mg	midazolam AUC ↑ 1.2-fold on Day 1

A difference of less than 2-fold increase of midazolam AUC is not considered clinically important.

Corticosteroids:

Dexamethasone: EMEND, when given as a regimen of 125 mg on Day 1 and 80 mg/day on Days 2 through 5, coadministered with 20-mg dexamethasone on Day 1 and 8-mg dexamethasone on Days 2 through 5, increased the AUC of dexamethasone by 2.2-fold on Days 1 and 5 *[see Dosage and*

Administration (2.1)]. A single dose of EMEND (40 mg) when coadministered with a single dose of dexamethasone 20 mg, increased the AUC of dexamethasone by 1.45-fold, which is not considered clinically significant.

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 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. Although the concomitant administration of methylprednisolone with the single 40-mg dose of EMEND has not been studied, a single 40-mg dose of EMEND produces a weak inhibition of CYP3A4 (based on midazolam interaction study) and it is not expected to alter the plasma concentrations of methylprednisolone to a clinically significant degree.

Chemotherapeutic agents:

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

Vinorelbine: In a pharmacokinetic study, EMEND (125-mg/80-mg regimen) did not influence the pharmacokinetics of vinorelbine to a clinically significant degree.

Oral contraceptives: When EMEND was administered as a 3-day regimen (125-mg/80-mg/80-mg) with ondansetron and dexamethasone, and coadministered with an oral contraceptive containing ethinyl estradiol and norethindrone, the trough concentrations of both ethinyl estradiol and norethindrone were reduced by as much as 64% for 3 weeks post-treatment.

When a daily dosage of an oral contraceptive containing ethinyl estradiol and norgestimate was administered on Days 1 through 21, and EMEND 40 mg was given on Day 8, the AUC of ethinyl estradiol decreased by 4% and by 29% on Day 8 and Day 12, respectively, while the AUC of norelgestromin increased by 18% on Day 8 and decreased by 10% on Day 12. In addition, the trough concentrations of ethinyl estradiol and norelgestromin on Days 8 through 21 were generally lower following coadministration of the oral contraceptive with EMEND 40 mg on Day 8 compared to the trough levels following administration of the oral contraceptive alone *[see Drug Interactions (7.1)]*.

CYP2C9 substrates (e.g., 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 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 *[see Drug Interactions (7.1)]*.

Tolbutamide: EMEND, when given as 125 mg on Day 1 and 80 mg/day on Days 2 and 3, decreased the AUC of tolbutamide by 23% on Day 4, 28% on Day 8, and 15% on Day 15, when a single dose of tolbutamide 500 mg was administered prior to the administration of the 3-day regimen of EMEND and on Days 4, 8, and 15. This effect was not considered clinically important.

EMEND, when given as a 40-mg single dose on Day 1, decreased the AUC of tolbutamide by 8% on Day 2, 16% on Day 4, 15% on Day 8, and 10% on Day 15, when a single dose of tolbutamide 500 mg was administered prior to the administration of EMEND 40 mg and on Days 2, 4, 8, and 15. This effect was not considered significant.

P-glycoprotein substrates: 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).

Effect of Other Drugs on the Pharmacokinetics of Aprepitant

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 *[see Drug Interactions (7.2)]*.

Rifampin: When a single 375-mg dose of EMEND (3 times the maximum recommended dose) 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 *[see Drug Interactions (7.2)]*.

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 (approximately 1.8 times the recommended dose), 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 *[see Drug Interactions (7.2)]*.

Paroxetine: Coadministration of once daily doses of aprepitant, as a tablet formulation comparable to 85 mg or 170 mg of the capsule formulation (approximately 0.7 and 1.4 times the maximum recommended dose), 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. This effect was not considered clinically important.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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 (AUC) of 0.7 to 1.6 times the adult human exposure at the 125-mg/80-mg/80-mg EMEND regimen. 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 adult human exposure at the 125-mg/80-mg/80-mg EMEND regimen. Treatment with aprepitant produced skin fibrosarcomas at 125 and 500 mg/kg/day doses in male mice.

Mutagenesis

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.

Impairment of Fertility

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 adult human dose and exposure in female rats at about 1.6 times the adult human exposure at the 125-mg/80-mg/80-mg EMEND regimen).

14 CLINICAL STUDIES

14.1 Prevention of Nausea and Vomiting Associated with HEC in Adults

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

In Studies 1 and 2, both multicenter, randomized, parallel, double-blind, controlled clinical studies in adults, EMEND in combination with ondansetron and dexamethasone was compared with standard therapy (ondansetron and dexamethasone alone) in patients receiving a chemotherapy regimen that included cisplatin greater than 50 mg/m^2 (mean cisplatin dose = 80.2 mg/m^2). See Table 13.

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

Of the 550 patients who were randomized to receive the EMEND regimen, 42% were women, 58% men, 59% White, 3% Asian, 5% Black, 12% Hispanic American, and 21% Multi-Racial. The EMEND-treated patients in these clinical studies ranged from 14 to 84 years of age, with a mean age of 56 years. A total of 170 patients were 65 years or older, with 29 patients being 75 years or older.

Table 13: HEC Treatment Regimens – Studies 1 and 2*

	Day 1	Day 2	Day 3	Day 4
CINV EMEND Regimen				
Oral EMEND†	125 mg	80 mg	80 mg	none
Oral Dexamethasone‡	12 mg	8 mg	8 mg	8 mg
Ondansetron	5-HT$_3$ antagonist§	none	none	none
CINV Standard Therapy				
Oral Dexamethasone	20 mg	8 mg twice daily	8 mg twice daily	8 mg twice daily
Ondansetron	5-HT$_3$ antagonist§	none	none	none

*EMEND placebo and dexamethasone placebo were used to maintain blinding.
†EMEND was administered 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 12 mg dose of dexamethasone on Day 1 reflects a dosage adjustment to account for a drug interaction with the EMEND regimen *[see Clinical Pharmacology (12.3)]*.
§Ondansetron 32 mg intravenous was used in the clinical trials of EMEND. Although this dose was used in clinical trials, this is no longer the currently recommended dose. Refer to the ondansetron prescribing information for the current recommended dose.

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 in which emetic episodes included vomiting, retching, or dry heaves:

Primary endpoint:
- complete response (defined as no emetic episodes and no use of rescue therapy as recorded in patient diaries)

Other prespecified endpoints:
- complete protection (defined as no emetic episodes, no use of rescue therapy, and a maximum nausea visual analogue scale [VAS] score less than 25 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 less than 5 mm on a 0 to 100 mm scale)
- no significant nausea (maximum VAS less than 25 mm on a 0 to 100 mm scale)

A summary of the key study results from each individual study analysis is shown in Table 14. In both studies, a statistically significantly higher proportion of patients receiving the EMEND regimen in Cycle 1 had a complete response in the overall phase (primary endpoint), compared with patients receiving standard therapy. A statistically significant difference in complete response in favor of the EMEND regimen was also observed when the acute phase and the delayed phase were analyzed separately.

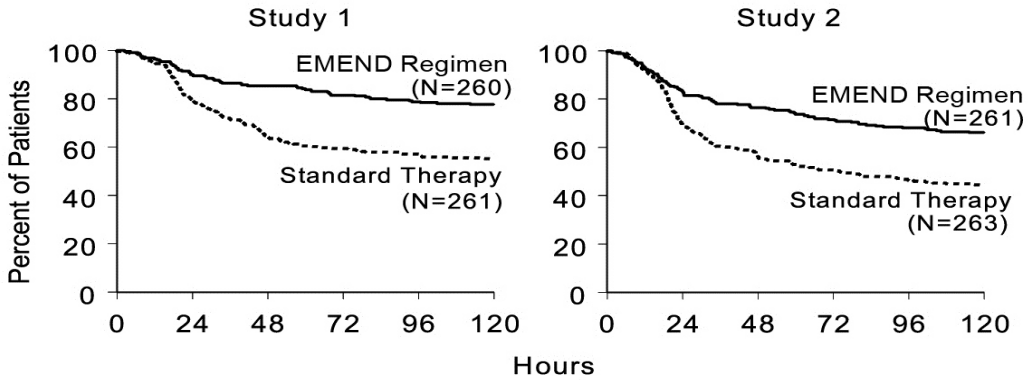
Table 14: Percent of Patients Receiving HEC Responding by Treatment Group and Phase — Cycle 1

	Study 1			Study 2		
ENDPOINTS	**EMEND Regimen (N=260)* %**	**Standard Therapy (N=261)* %**	**p-Value**	**EMEND Regimen (N=261)* %**	**Standard Therapy (N=263)* %**	**p-Value**
PRIMARY ENDPOINT						
Complete Response						
Overall[†]	73	52	<0.001	63	43	<0.001
OTHER PRESPECIFIED ENDPOINTS						
Complete Response						
Acute phase[‡]	89	78	<0.001	83	68	<0.001
Delayed phase[§]	75	56	<0.001	68	47	<0.001
Complete Protection						
Overall	63	49	0.001	56	41	<0.001
Acute phase	85	75	NS[¶]	80	65	<0.001
Delayed phase	66	52	<0.001	61	44	<0.001
No Emesis						
Overall	78	55	<0.001	66	44	<0.001
Acute phase	90	79	0.001	84	69	<0.001
Delayed phase	81	59	<0.001	72	48	<0.001
No Nausea						
Overall	48	44	NS[#]	49	39	NS[¶]
Delayed phase	51	48	NS[#]	53	40	NS[¶]
No Significant Nausea						
Overall	73	66	NS[#]	71	64	NS[#]
Delayed phase	75	69	NS[#]	73	65	NS[#]

Visual analogue scale (VAS) score range: 0 mm=no nausea; 100 mm=nausea as bad as it could be.
*N: Number of patients (older than 18 years of age) 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.
[¶]Not statistically significant when adjusted for multiple comparisons.
[#]Not statistically significant.

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

Figure 1: Percent of Patients Receiving HEC Who Remain Emesis Free Over Time — Cycle 1

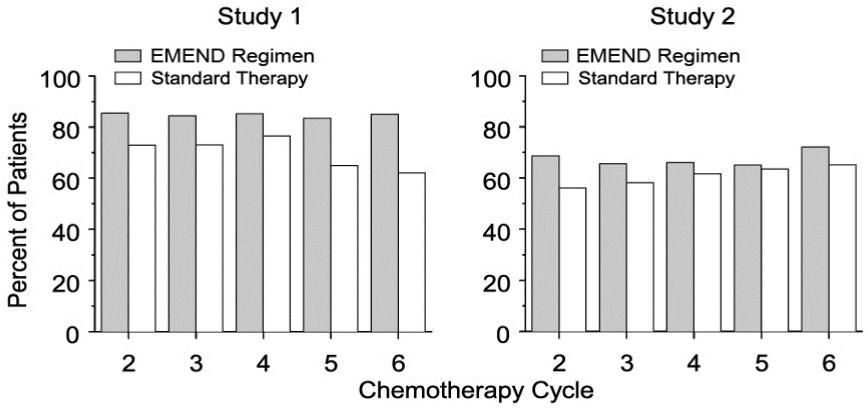


p-Value <0.001 based on a log rank test for Study 1 and Study 2; nominal p-values not adjusted for multiplicity.

Additional Patient-Reported Outcomes: The impact of nausea and vomiting on patients' daily lives was assessed in Cycle 1 of both 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 greater than 108. In each of the 2 studies, a higher proportion of patients receiving the EMEND 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 EMEND regimen was maintained throughout repeat cycles for those patients continuing in each of the multiple cycles.

Figure 2: Proportion of Patients Receiving HEC with No Emesis and No Significant Nausea by Treatment Group and Cycle



	Study 1					Study 2				
EMEND (N)	158	122	81	54	40	191	148	103	63	43
Standard (N)	177	111	68	37	**29**	216	167	112	74	**43**

14.2 Prevention of Nausea and Vomiting Associated with MEC in Adults

EMEND was studied in two randomized, double-blind, parallel-group studies (Studies 3 and 4) in adult patients receiving MEC.

In Study 3, in breast cancer patients, EMEND in combination with ondansetron and dexamethasone was compared with standard therapy (ondansetron and dexamethasone) in patients receiving a MEC regimen that included cyclophosphamide 750-1500 mg/m^2; or cyclophosphamide 500-

1500 mg/m^2 and doxorubicin (less than or equal to 60 mg/m^2) or epirubicin (less than or equal to 100 mg/m^2). See Table 15.

In this study, the most common combinations were cyclophosphamide + doxorubicin (61%); and cyclophosphamide + epirubicin + fluorouracil (22%).

Of the 438 patients who were randomized to receive the EMEND regimen, 99.5% were women. Of these, approximately 80% were White, 8% Black, 8% Asian, 4% Hispanic, and less than 1% Other. The EMEND-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.

Table 15: MEC Treatment Regimens – Studies 3 and 4*

	Day 1	Day 2	Day 3
CINV EMEND Regimen			
Oral EMEND†	125 mg	80 mg	80 mg
Oral Dexamethasone	12 mg‡	none	none
Oral Ondansetron	8 mg x 2 doses§	none	none
CINV Standard Therapy			
Oral Dexamethasone	20 mg‡	none	none
Oral Ondansetron	8 mg x 2 doses§	8 mg twice daily	8 mg twice daily

*EMEND placebo and dexamethasone placebo were used to maintain blinding.
†EMEND was administered 1 hour prior to chemotherapy treatment on Day 1 and in the mornings on Days 2 and 3.
‡Dexamethasone was administered 30 minutes prior to chemotherapy treatment on Day 1. The 12 mg dose of dexamethasone on Day 1 reflects a dosage adjustment to account for a drug interaction with the EMEND regimen *[see Clinical Pharmacology (12.3)]*.
§The first ondansetron dose was administered 30 to 60 minutes prior to chemotherapy treatment on Day 1 and the second dose was administered 8 hours after first ondansetron dose.

The antiemetic activity of EMEND was evaluated based on the following endpoints in which emetic episodes included vomiting, retching, or dry heaves:

Primary endpoint:

- complete response (defined as no emetic episodes and no use of rescue therapy as recorded in patient diaries) 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 less than 5 mm on a 0 to 100 mm scale)
- no significant nausea (maximum VAS less than 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 less than 25 mm on a 0 to 100 mm scale)
- complete response during the acute and delayed phases.

A summary of the key results from Study 3 is shown in Table 16. In Study 3, a statistically significantly (p=0.015) higher proportion of patients receiving the EMEND 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 primarily driven by the “No Emesis Endpoint”, a principal component of this composite primary endpoint. In addition, a higher proportion of patients receiving the EMEND 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.

Table 16: Percent of Patients Receiving MEC Responding by Treatment Group and Phase — Cycle 1 of Study 3

ENDPOINTS	EMEND Regimen (N=433)* %	Standard Therapy (N=424)* %	p-Value
PRIMARY ENDPOINT†			
Complete Response	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

*N: Number of patients included in the primary analysis of complete response.
†Overall: 0 to 120 hours post-chemotherapy treatment.
‡NS when adjusted for prespecified multiple comparisons rule; unadjusted p-value <0.001.

Additional Patient-Reported Outcomes: In Study 3, in patients receiving MEC, 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 EMEND 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: In Study 3, patients receiving MEC were permitted to continue into the Multiple-Cycle extension of the study for up to 3 additional cycles of chemotherapy. The antiemetic effect for patients receiving the EMEND regimen was maintained during all cycles.

In Study 4, EMEND in combination with ondansetron and dexamethasone was compared with a standard therapy (ondansetron and dexamethasone alone) in patients receiving a MEC regimen that included any intravenous dose of oxaliplatin, carboplatin, epirubicin, idarubicin, ifosfamide, irinotecan, daunorubicin, doxorubicin; cyclophosphamide intravenous (less than 1500 mg/m^2); or cytarabine intravenous (greater than 1 g/m^2). See Table 15. Patients receiving the EMEND regimen were receiving chemotherapy for a variety of tumor types including 50% with breast cancer, 21% with gastrointestinal cancers including colorectal cancer, 13% with lung cancer and 6% with gynecological cancers.

Of the 430 patients who were randomized to receive the EMEND regimen, 76% were women and 24% were men. The distribution by race was 67% White, 6% Black or African American, 11% Asian, and 12% multiracial. Classified by ethnicity, 36% were Hispanic and 64% were non-Hispanic. The EMEND-treated patients in this clinical study ranged from 22 to 85 years of age, with a mean age of 57 years; approximately 59% of the patients were 55 years or older with 32 patients being over 74 years.

The antiemetic activity of EMEND was evaluated based on no vomiting (with or without rescue therapy) in the overall period (0 to 120 hours post-chemotherapy) and complete response (defined as no vomiting and no use of rescue therapy) in the overall period.

A summary of the key results from Study 4 is shown in Table 17. In Study 4, a statistically significantly higher proportion of patients receiving the EMEND regimen (76%) in Cycle 1 had no vomiting during the overall phase compared with patients receiving standard therapy (62%). In addition, a higher proportion of patients receiving the EMEND regimen (69%) in Cycle 1 had a complete response in the overall phase (0-120 hours) compared with patients receiving standard therapy (56%). In the acute phase (0 to 24 hours following initiation of chemotherapy), a higher proportion of patients receiving EMEND compared to patients receiving standard therapy were observed to have no vomiting (92% and 84%, respectively) and complete response (89% and 80%, respectively). In the delayed phase (25 to 120 hours following initiation of chemotherapy), a higher proportion of patients receiving EMEND compared to patients receiving standard therapy were observed to have no vomiting (78% and 67%, respectively) and complete response (71% and 61%, respectively).

In a subgroup analysis by tumor type, a numerically higher proportion of patients receiving EMEND were observed to have no vomiting and complete response compared to patients receiving standard therapy. For sex, the difference in complete response rates between the EMEND and standard regimen

groups was 14% in females (64.5% and 50.3%, respectively) and 4% in males (82.2% and 78.2%, respectively) during the overall phase. A similar difference for sex was observed for the no vomiting endpoint.

Table 17: Percent of Patients Receiving MEC Responding by Treatment Group — Cycle 1 of Study 4

ENDPOINTS	EMEND Regimen (N=430)* %	Standard Therapy (N=418)* %	p-Value
No Vomiting Overall	76	62	<0.0001
Complete Response Overall	69	56	0.0003

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

14.3 Prevention of Nausea and Vomiting Associated with HEC or MEC in Pediatric Patients

In a randomized, double-blind, active comparator-controlled clinical study that included 302 pediatric patients aged 6 months to 17 years receiving HEC or MEC, EMEND in combination with ondansetron was compared to ondansetron alone (control regimen) for the prevention of CINV (Study 5). Intravenous dexamethasone was permitted as part of the antiemetic regimen in both treatment groups, at the discretion of the physician. A 50% dose reduction of dexamethasone was required for patients in the EMEND group, reflecting a dosage adjustment to account for a drug interaction *[see Clinical Pharmacology (12.3)].* No dexamethasone dose reduction was required for patients who received the control regimen.

Eligible patients had documented malignancy at either an original diagnosis or relapse and were scheduled to receive emetogenic chemotherapy or a chemotherapy regimen not previously tolerated due to vomiting along with ondansetron as part of their antiemetic regimen.

Of the 152 pediatric patients randomized to receive the EMEND regimen, 55% were male, 45% female, 78% White, 7% Asian, 0% Black, 24% Hispanic, and 13% Multi-Racial. The most common primary malignancies in subjects receiving the EMEND regimen were osteosarcoma (11%), Ewing's sarcoma (11%), neuroblastoma (9%) and rhabdomyosarcoma (8%). Other concomitant chemotherapy agents commonly administered and the number of EMEND patients exposed were: vincristine sulfate (65), etoposide (59), doxorubicin (48), ifosfamide (45), carboplatin (39), and cisplatin (35).

The treatment regimens in Study 5 for pediatric patients are defined in Table 18. Of the pediatric patients, 29% in the EMEND regimen and 28% in the control regimen used dexamethasone as part of the antiemetic regimen in Cycle 1.

Table 18: HEC and MEC Treatment Regimens* for Pediatric Patients 6 Months to 17 Years of Age— Study 5

	Day 1	Day 2	Day 3
CINV EMEND Regimen			
Pediatric Patients 6 Months to less than 12 Years of Age[†]	3 mg/kg body weight oral suspension	2 mg/kg body weight oral suspension	2 mg/kg body weight oral suspension
Pediatric Patients 12 to 17 Years of Age[†]	125 mg capsule	80 mg capsule	80 mg capsule
Ondansetron	Per standard of care[‡]	none	none
CINV Control Regimen[§]			
Ondansetron	Per standard of care[‡]	none	none

*Intravenous dexamethasone was permitted at the discretion of the physician. A 50% dose reduction of dexamethasone was required for patients in the EMEND group, reflecting a dosage adjustment to account for a drug interaction *[see Clinical Pharmacology (12.3)].* No dexamethasone dose reduction was required for patients in the control regimen.
[†]EMEND was administered 1 hour prior to chemotherapy treatment on Days 1, 2, and 3. If no chemotherapy was given on Days 2 and 3, EMEND was administered in the morning.
[‡]Ondansetron was administered 30 minutes prior to chemotherapy on Day 1
[§]EMEND placebo was used to maintain blinding.

The antiemetic activity of EMEND was evaluated over a 5-day (120 hour) period following the initiation of chemotherapy on Day 1. The primary endpoint in Study 5 was complete response in the delayed phase (25 to 120 hours following chemotherapy) in Cycle 1. Patients had the opportunity to receive open-label EMEND in subsequent cycles (Optional Cycles 2-6); however efficacy was not assessed in these optional cycles. Overall efficacy was based on the evaluation of the following endpoints:

Primary endpoint:

- complete response (no vomiting, retching and no use of rescue medication) in the delayed phase (25 to 120 hours following initiation of chemotherapy)

Other prespecified endpoints:

- complete response in the acute phase (0 to 24 hours following initiation of chemotherapy)
- complete response in the overall phase (up to 120 hours following initiation of chemotherapy)
- no vomiting (defined as no emesis, retching or dry heaves, regardless of use of rescue medication) in the overall phase
- safety and tolerability

A summary of the key study results are shown in Table 19.

Table 19: Percent of Patients Who Responded to Treatment by Treatment Group and Phase – Cycle 1 of Study 5

	EMEND Regimen n/m (%)	Control Regimen n/m (%)
PRIMARY ENDPOINT		
Complete Response* - Delayed phase	77/152 (50.7)[†]	39/150 (26.0)
OTHER PRESPECIFIED ENDPOINTS		
Complete Response* – Acute phase	101/152 (66.4)[‡]	78/150 (52.0)
Complete Response* – Overall phase	61/152 (40.1)[†]	30/150 (20.0)

*Complete Response = No vomiting or retching and no use of rescue medication.
[†]p<0.01 when compared to Control Regimen
[‡] p<0.05 when compared to Control Regimen
n/m = Number of patients with desired response/number of patients included in time point.
Acute Phase: 0 to 24 hours following initiation of chemotherapy.
Delayed Phase: 25 to 120 hours following initiation of chemotherapy.
Overall Phase: 0 to 120 hours following initiation of chemotherapy.

14.4 Prevention of PONV in Adults

In two multicenter, randomized, double-blind, active comparator-controlled, parallel-group clinical studies (Studies 7 and 8), EMEND was compared with ondansetron for the prevention of postoperative nausea and vomiting in 1658 patients undergoing open abdominal surgery. These two studies were of similar design; however, they differed in terms of study hypothesis, efficacy analyses and geographic location. Study 7 was a multinational study including the U.S., whereas, Study 8 was conducted entirely in the U.S.

In the two studies, patients were randomized to receive 40-mg EMEND, 125-mg EMEND, or 4-mg ondansetron as a single dose. EMEND was given orally with 50 mL of water 1 to 3 hours before anesthesia. Ondansetron was given intravenously immediately before induction of anesthesia. A comparison between the EMEND 125-mg dose did not demonstrate any additional clinical benefit over the 40-mg dose and is not a recommended dosage regimen *[see Dosage and Administration (2.2)]*.

Of the 564 patients who received 40-mg EMEND, 92% were women and 8% were men; of these, 58% were White, 13% Hispanic American, 7% Multi-Racial, 14% Black, 6% Asian, and 2% Other. The age of patients treated with 40-mg EMEND ranged from 19 to 84 years, with a mean age of 46.1 years. 46 patients were 65 years or older, with 13 patients being 75 years or older.

The antiemetic activity of EMEND was evaluated during the 0 to 48 hour period following the end of surgery.

Efficacy measures in Study 7 included:

- no emesis (defined as no emetic episodes regardless of use of rescue therapy) in the 0 to 24 hours following the end of surgery (primary)
- complete response (defined as no emetic episodes and no use of rescue therapy) in the 0 to 24 hours following the end of surgery (primary)
- no emesis (defined as no emetic episodes regardless of use of rescue therapy) in the 0 to 48 hours following the end of surgery (secondary)
- time to first use of rescue medication in the 0 to 24 hours following the end of surgery (exploratory)
- time to first emesis in the 0 to 48 hours following the end of surgery (exploratory).

A closed testing procedure was applied to control the type I error for the primary endpoints.

The results of the primary and secondary endpoints for 40-mg EMEND and 4-mg ondansetron are described in Table 20:

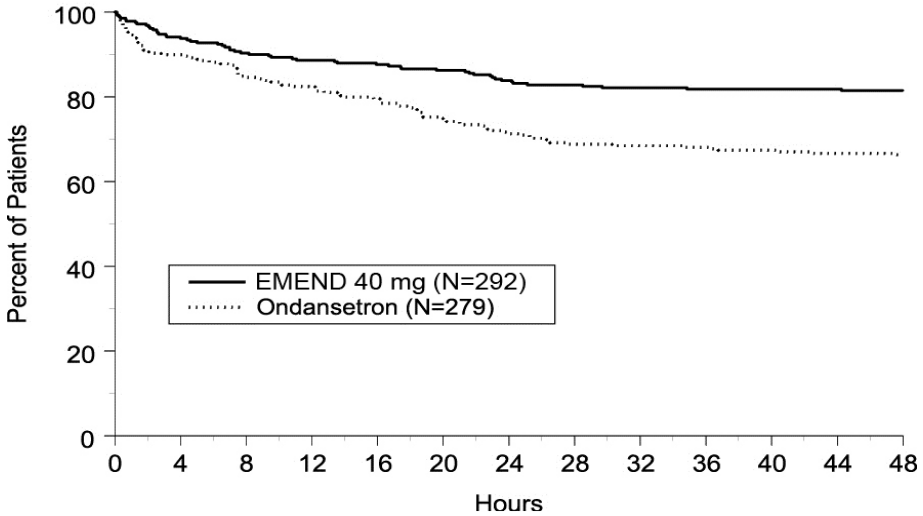
Table 20: Response Rates for Select Efficacy Endpoints (Modified-Intention-to-Treat Population) – Study 7

Treatment	n/m (%)	EMEND vs. Ondansetron		
		Δ	Odds ratio*	Analysis
PRIMARY ENDPOINTS				
No Vomiting 0 to 24 hours (Superiority) (no emetic episodes)				
EMEND 40 mg	246/293 (84.0)	12.6%	2.1	P<0.001†
Ondansetron	200/280 (71.4)			
Complete Response (Non-inferiority: If LB‡ >0.65) (no emesis and no rescue therapy, 0 to 24 hours)				
EMEND 40 mg	187/293 (63.8)	8.8%	1.4	LB=1.02
Ondansetron	154/280 (55.0)			
Complete Response (Superiority: If LB >1.0) (no emesis and no rescue therapy, 0 to 24 hours)				
EMEND 40 mg	187/293 (63.8)	8.8%	1.4	LB=1.02‡
Ondansetron	154/280 (55.0)			
SECONDARY ENDPOINT				
No Vomiting 0 to 48 hours (Superiority) (no emetic episodes)				
EMEND 40 mg	238/292 (81.5)	15.2%	2.3	P<0.001§
Ondansetron	185/279 (66.3)			

n/m = Number of responders/number of patients in analysis.
Δ Difference (%):EMEND 40 mg minus Ondansetron.
*Estimated odds ratio for EMEND versus Ondansetron. A value of >1 favors EMEND over Ondansetron.
†P-value of two-sided test <0.05.
‡LB = lower bound of 1-sided 97.5% confidence interval for the odds ratio.
§Based on the prespecified fixed sequence multiplicity strategy, EMEND 40 mg was not superior to Ondansetron.

In Study 7, the use of EMEND did not affect the time to first use of rescue medication when compared to ondansetron. However, compared to the ondansetron group, use of EMEND delayed the time to first vomiting, as depicted in Figure 3.

Figure 3: Percent of Patients Who Remain Emesis Free During the 48 Hours Following End of Surgery – Study 7



Efficacy measures in Study 8 included:

- complete response (defined as no emetic episodes and no use of rescue therapy) in the 0 to 24 hours following the end of surgery (primary)
- no emesis (defined as no emetic episodes regardless of use of rescue therapy) in the 0 to 24 hours following the end of surgery (secondary)
- no use of rescue therapy in the 0 to 24 hours following the end of surgery (secondary)
- no emesis (defined as no emetic episodes regardless of use of rescue therapy) in the 0 to 48 hours following the end of surgery (secondary).

Study 8 failed to satisfy its primary hypothesis that EMEND is superior to ondansetron in the prevention of PONV as measured by the proportion of patients with complete response in the 24 hours following end of surgery.

The study demonstrated that 40-mg EMEND had a clinically meaningful effect with respect to the secondary endpoint "no vomiting" during the first 24 hours after surgery and was associated with a 16% improvement over ondansetron for the no vomiting endpoint.

Table 21: Response Rates for Select Efficacy Endpoints (Modified-Intention-to-Treat Population) – Study 8

Treatment	n/m (%)	EMEND vs. Ondansetron		
		Δ	Odds ratio*	Analysis
PRIMARY ENDPOINT				
Complete Response (no emesis and no rescue therapy, 0 to 24 hours)				
EMEND 40 mg	111/248 (44.8)	2.5%	1.1	0.61
Ondansetron	104/246 (42.3)			
SECONDARY ENDPOINTS				
No Vomiting (no emetic episodes, 0 to 24 hours)				
EMEND 40 mg	223/248 (89.9)	16.3%	3.2	<0.001†
Ondansetron	181/246 (73.6)			
No Use of Rescue Medication (for established emesis or nausea, 0 to 24 hours)				
EMEND 40 mg	112/248 (45.2)	-0.7%	1.0	0.83
Ondansetron	113/246 (45.9)			
No Vomiting 0 to 48 hours (Superiority) (no emetic episodes, 0 to 48 hours)				
EMEND 40 mg	209/247 (84.6)	17.7%	2.7	<0.001*
Ondansetron	164/245 (66.9)			

n/m = Number of responders/number of patients in analysis.
Δ Difference (%):EMEND 40 mg minus Ondansetron.
*Estimated odds ratio: EMEND 40 mg versus Ondansetron.
†Not statistically significant after pre-specified multiplicity adjustment.

16 HOW SUPPLIED/STORAGE AND HANDLING

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 0006-0462-06 unit-dose package of 6.

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 0006-0461-02 unit-of-use BiPack of 2

NDC 0006-0461-06 unit-dose package of 6.

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

NDC 0006-3862-03.

No. 6741 — 40-mg capsules: Opaque, hard gelatin capsule with white body and mustard yellow cap with “464” and “40 mg” printed radially in black ink on the body. They are supplied as follows:

NDC 0006-0464-10 unit-of-use package of 1

NDC 0006-0464-05 unit-dose package of 5.

No. 3066 — 125 mg for oral suspension: Pink to light pink powder, in a single-use pouch, packaged as a kit with one 1 mL oral dosing dispenser, one 5 mL oral dosing dispenser, one cap and one mixing cup. It is supplied as follows:

NDC 0006-3066-03 – unit of use carton.

Storage and Handling

Capsules

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

For Oral Suspension

Store unopened pouch at 20-25°C (68-77°F); excursions permitted between 15-30°C (between 59-86°F). Store in the original container. Do not open pouch until ready for use.

Once prepared, if suspension is not used immediately, store refrigerated [between 36°F-46°F (2°C-8°C)] for up to 72 hours prior to use. When ready to use, the mixture can be kept at room temperature [between 68°F-77°F (20°C-25°C)] for up to 3 hours.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Hypersensitivity Reactions

Advise patients that hypersensitivity reactions, including anaphylaxis, have been reported in patients taking EMEND. Advise patients to stop taking EMEND and seek immediate medical attention if they experience signs or symptoms of a hypersensitivity reaction, such as hives, rash and itching, skin peeling or sores, or difficulty in breathing or swallowing.

Drug Interactions

Advise patients to discuss all medications they are taking, including other prescription, non-prescription medication or herbal products *[see Contraindications (4), Warnings and Precautions (5.1)].*

Warfarin: Instruct patients on chronic warfarin therapy to follow instructions from their healthcare provider regarding blood draws to monitor their INR during the 2-week period, particularly at 7 to 10 days, following initiation of the 3-day regimen of EMEND with each chemotherapy cycle, or following administration of a single 40-mg dose of EMEND for the prevention of postoperative nausea and vomiting *[see Warnings and Precautions (5.2)]*.

Hormonal Contraceptives: Advise patients that administration of EMEND may reduce the efficacy of hormonal contraceptives. Instruct patients to use effective alternative or back-up methods of contraception (such as condoms and spermicides) during treatment with EMEND and for 1 month following the last dose of EMEND *[see Warnings and Precautions (5.3), Use in Specific Populations (8.3)]*.

Distributed by:
Merck Sharp & Dohme Corp., a subsidiary of **MERCK & CO., INC.,** Whitehouse Station, NJ 08889, USA

For patent information: www.merck.com/product/patent/home.html

uspi-mk0869-mf-1901r012