HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use EMEND safely and effectively. See full prescribing information for EMEND.

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

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

EMEND® is a substance P/neurokinin 1 (NK_1) receptor antagonist, indicated:

- in combination with other antiemetic agents 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 (1.1)
  - prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC) (1.1)
- for the prevention of postoperative nausea and vomiting (PONV) (1.2)

Limitations of Use (1.3)

- Not studied for the treatment of established nausea and vomiting.
- Chronic continuous administration is not recommended.

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

Prevention of Chemotherapy Induced Nausea and Vomiting (2.1)

- EMEND is given for 3 days as part of the chemotherapy induced nausea and vomiting (CINV) regimen that includes a corticosteroid and a 5-HT_3 antagonist. (2.1)
  - The recommended dose of EMEND is 125 mg orally 1 hour prior to chemotherapy treatment (Day 1) and 80 mg orally once daily in the morning on Days 2 and 3. (2.1)
  - EMEND (fosaprepitant dimeglumine) for Injection may be substituted for oral EMEND (125 mg) on Day 1 only as part of the CINV regimen. (2.1)

Prevention of Postoperative Nausea and Vomiting (2.2)

- The recommended oral dosage of EMEND for the postoperative nausea and vomiting (PONV) indication is 40 mg within 3 hours prior to induction of anesthesia. (2.2)

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

Capsules: 40 mg; 80 mg; 125 mg (3)

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

- Hypersensitivity to any component of this medication. (4, 6.2)
- EMEND should not be used concurrently with pimozide, terfenadine, astemizole, or cisapride, since inhibition of CYP3A4 by aprepitant could result in elevated plasma concentrations of these drugs, potentially causing serious or life-threatening reactions. (4)

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

- Coadministration of aprepitant with warfarin (a CYP2C9 substrate) may result in a clinically significant decrease in International Normalized Ratio (INR) of prothrombin time. (5.2)
- The efficacy of hormonal contraceptives during and for 28 days following the last dose of EMEND may be reduced. Alternative or back-up methods of contraception should be used. (5.3, 7.1)
- EMEND is a dose-dependent inhibitor of CYP3A4, and should be used with caution in patients receiving concomitant medications that are primarily metabolized through CYP3A4. (5.1)
- Caution should be exercised when administered in patients with severe hepatic impairment. (2.5, 5.4, 12.3)

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

- Clinical adverse experiences for the CINV regimen in conjunction with highly and moderately emetogenic chemotherapy (incidence >10%) are: alopecia, anorexia, asthenia/fatigue, constipation, diarrhea, headache, hiccups, nausea. (6.1)
- Clinical adverse experiences for the PONV regimen (incidence >5%) are: constipation, hypotension, nausea, pruritus, pyrexia. (6.1)

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----------

- Aprepitant is a substrate for CYP3A4; therefore, coadministration of EMEND with drugs that inhibit or induce CYP3A4 activity may result in increased or reduced plasma concentrations of aprepitant, respectively. (5.1, 7.1, 7.2).
- Aprepitant is an inducer of CYP2C9; therefore, coadministration of EMEND with drugs that are metabolized by CYP2C9 (e.g., warfarin, tolbutamide), may result in lower plasma concentrations of these drugs. (5.2, 7.1)

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

Revised: 12/2012

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Prevention of Chemotherapy Induced Nausea and Vomiting (CINV)

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

- prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including high-dose cisplatin
- prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC) *[see Dosage and Administration (2.1)]*.

1.2 Prevention of Postoperative Nausea and Vomiting (PONV)

EMEND is indicated for the prevention of postoperative nausea and vomiting *[see Dosage and Administration (2.2)]*.

1.3 Limitations of Use

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

Chronic continuous administration is not recommended *[see Warnings and Precautions (5.5)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Prevention of Chemotherapy Induced Nausea and Vomiting (CINV)

Capsules of EMEND (aprepitant) are given for 3 days as part of a regimen that includes a corticosteroid and a 5-HT_3 antagonist. The recommended dose of EMEND is 125 mg orally 1 hour prior to chemotherapy treatment (Day 1) and 80 mg orally once daily in the morning on Days 2 and 3. The package insert for the co-administered 5-HT_3 antagonist must be consulted prior to initiation of treatment with EMEND.

EMEND may be taken with or without food.

EMEND (fosaprepitant dimeglumine) for Injection (115 mg) is a prodrug of aprepitant and may be substituted for oral EMEND (125 mg), 30 minutes prior to chemotherapy, on Day 1 only of the CINV regimen as an intravenous infusion administered over 15 minutes.

The following regimen should be used for the prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy:

	Day 1	Day 2	Day 3	Day 4
EMEND*	125 mg orally	80 mg orally	80 mg orally	none
Dexamethasone**	12 mg orally	8 mg orally	8 mg orally	8 mg orally
5-HT_3 antagonist	See the package insert for the selected 5-HT_3 antagonist for appropriate dosing information.	none	none	none

*EMEND is administered orally 1 hour prior to chemotherapy treatment on Day 1 and in the morning on Days 2 and 3.
**Dexamethasone is administered 30 minutes prior to chemotherapy treatment on Day 1 and in the morning on Days 2 through 4. The dose of dexamethasone accounts for drug interactions.

The following regimen should be used for the prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy:

	Day 1	Day 2	Day 3
EMEND*	125 mg orally	80 mg orally	80 mg orally
Dexamethasone**	12 mg orally	none	none
5-HT_3 antagonist	See the package insert for the selected 5-HT_3 antagonist for appropriate dosing	none	none

	information.		

*EMEND is administered orally 1 hour prior to chemotherapy treatment on Day 1 and in the morning on Days 2 and 3.
**Dexamethasone is administered 30 minutes prior to chemotherapy treatment on Day 1. The dose of dexamethasone accounts for drug interactions.

2.2 Prevention of Postoperative Nausea and Vomiting (PONV)

The recommended oral dosage of EMEND is 40 mg within 3 hours prior to induction of anesthesia. EMEND may be taken with or without food.

2.3 Geriatric Patients

No dosage adjustment is necessary for the elderly.

2.4 Patients with Renal Impairment

No dosage adjustment is necessary for patients with renal impairment or for patients with end stage renal disease (ESRD) undergoing hemodialysis.

2.5 Patients with Hepatic Impairment

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

2.6 Coadministration with Other Drugs

For additional information on dose adjustment for corticosteroids when coadministered with EMEND, see *Drug Interactions (7.1)*.

Refer to the full prescribing information for coadministered antiemetic agents.

3 DOSAGE FORMS AND STRENGTHS

- Capsules EMEND 40 mg are opaque, hard, gelatin capsules, with white body and mustard yellow cap with “464” and “40 mg” printed radially in black ink on the body.
- Capsules EMEND 80 mg are white, opaque, hard, gelatin capsules, with “461” and “80 mg” printed radially in black ink on the body.
- Capsules EMEND 125 mg are opaque, hard, gelatin capsules, with white body and pink cap with “462” and “125 mg” printed radially in black ink on the body.

4 CONTRAINDICATIONS

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

EMEND is a dose-dependent inhibitor of cytochrome P450 isoenzyme 3A4 (CYP3A4). EMEND should not be used concurrently with pimozide, terfenadine, astemizole, or cisapride. Inhibition of CYP3A4 by aprepitant could result in elevated plasma concentrations of these drugs, potentially causing serious or life-threatening reactions *[see Drug Interactions (7.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 CYP3A4 Interactions

EMEND (aprepitant), a dose-dependent inhibitor of CYP3A4, should be used with caution in patients receiving concomitant medications that are primarily metabolized through CYP3A4. Moderate inhibition of CYP3A4 by aprepitant, 125-mg/80-mg regimen, could result in elevated plasma concentrations of these concomitant medications.

Weak inhibition of CYP3A4 by a single 40-mg dose of aprepitant is not expected to alter the plasma concentrations of concomitant medications that are primarily metabolized through CYP3A4 to a clinically significant degree.

When aprepitant is used concomitantly with another CYP3A4 inhibitor, aprepitant plasma concentrations could be elevated. When EMEND is used concomitantly with medications that induce CYP3A4 activity, aprepitant plasma concentrations could be reduced and this may result in decreased efficacy of EMEND *[see Drug Interactions (7.1)]*.

Chemotherapy agents that are known to be metabolized by CYP3A4 include docetaxel, paclitaxel, etoposide, irinotecan, ifosfamide, imatinib, vinorelbine, vinblastine and vincristine. In clinical studies, EMEND (125-mg/80-mg regimen) was administered commonly with etoposide, vinorelbine, or paclitaxel. The doses of these agents were not adjusted to account for potential drug interactions.

In separate pharmacokinetic studies, no clinically significant change in docetaxel or vinorelbine pharmacokinetics was observed when EMEND (125-mg/80-mg regimen) was co-administered.

Due to the small number of patients in clinical studies who received the CYP3A4 substrates vinblastine, vincristine, or ifosfamide, particular caution and careful monitoring are advised in patients receiving these agents or other chemotherapy agents metabolized primarily by CYP3A4 that were not studied *[see Drug Interactions (7.1)]*.

5.2 Coadministration with Warfarin (a CYP2C9 substrate)

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

Upon coadministration with EMEND, the efficacy of hormonal contraceptives during and for 28 days following the last dose of EMEND may be reduced. Alternative or back-up methods of contraception should be used during treatment with EMEND and for 1 month following the last dose of EMEND *[see Drug Interactions (7.1)]*.

5.4 Patients with Severe Hepatic Impairment

There are no clinical or pharmacokinetic data in patients with severe hepatic impairment (Child-Pugh score >9). Therefore, caution should be exercised when EMEND is administered in these patients *[see Clinical Pharmacology (12.3) and Dosage and Administration (2.5)]*.

5.5 Chronic Continuous Use

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

6 ADVERSE REACTIONS

The overall safety of aprepitant was evaluated in approximately 5300 individuals.

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.

6.1 Clinical Trials Experience

Chemotherapy Induced Nausea and Vomiting

Highly Emetogenic Chemotherapy

In 2 well-controlled clinical trials in patients receiving highly emetogenic cancer chemotherapy, 544 patients were treated with aprepitant during Cycle 1 of chemotherapy and 413 of these patients continued into the Multiple-Cycle extension for up to 6 cycles of chemotherapy. EMEND was given in combination with ondansetron and dexamethasone.

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

Table 1
Percent of Patients Receiving Highly Emetogenic Chemotherapy with Clinical Adverse Experiences (Incidence ≥3%) — Cycle 1

	Aprepitant Regimen	Standard Therapy

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

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

Moderately Emetogenic Chemotherapy

During Cycle 1 of 2 moderately emetogenic chemotherapy studies, 868 patients were treated with the aprepitant regimen and 686 of these patients continued into extensions for up to 4 cycles of chemotherapy. In the combined analysis of Cycle 1 data for these 2 studies, adverse experiences were reported in approximately 69% of patients treated with the aprepitant regimen compared with approximately 72% of patients treated with standard therapy.

In the combined analysis of Cycle 1 data for these 2 studies, the adverse experience profile in both moderately emetogenic chemotherapy studies was generally comparable to the highly emetogenic chemotherapy studies. Table 2 shows the percent of patients with clinical adverse experiences reported at an incidence ≥3%.

Table 2
Percent of Patients Receiving Moderately Emetogenic Chemotherapy with Clinical Adverse Experiences (Incidence ≥3%) — Cycle 1

	Aprepitant Regimen (N = 868)	Standard Therapy (N = 846)
Blood and Lymphatic System Disorders		
Neutropenia	5.8	5.6
Metabolism and Nutrition Disorders		
Anorexia	6.2	7.2
Psychiatric Disorders		
Insomnia	2.6	3.7
Nervous System Disorders		
Headache	13.2	14.3
Dizziness	2.8	3.4
Gastrointestinal Disorders		
Constipation	10.3	15.5
Diarrhea	7.6	8.7
Dyspepsia	5.8	3.8
Nausea	5.8	5.1
Stomatitis	3.1	2.7

Skin and Subcutaneous Tissue Disorders		
Alopecia	12.4	11.9
General Disorders and General Administration Site Conditions		
Fatigue	15.4	15.6
Asthenia	4.7	4.6

In a combined analysis of these two studies, isolated cases of serious adverse experiences were similar in the two treatment groups.

Highly and Moderately Emetogenic Chemotherapy

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

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

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

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

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

Psychiatric disorders: anxiety disorder, confusion, depression.

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

Eye disorders: conjunctivitis.

Cardiac disorders: myocardial infarction, palpitations, tachycardia.

Vascular disorders: deep venous thrombosis, flushing, hot flush, hypertension, hypotension.

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

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

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

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

Renal and urinary disorders: dysuria, renal insufficiency.

Reproductive system and breast disorders: pelvic pain.

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

Investigations: weight loss.

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

Laboratory Adverse Experiences

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

Table 3

Percent of Patients Receiving Highly Emetogenic Chemotherapy with Laboratory Adverse Experiences (Incidence ≥3%) — Cycle 1

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

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

The adverse experience profiles 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.

Postoperative Nausea and Vomiting

In well-controlled clinical studies in patients receiving general anesthesia, 564 patients were administered 40-mg aprepitant orally and 538 patients were administered 4-mg ondansetron IV.

Clinical adverse experiences were reported in approximately 60% of patients treated with 40-mg aprepitant compared with approximately 64% of patients treated with 4-mg ondansetron IV. Table 4 shows the percent of patients with clinical adverse experiences reported at an incidence ≥3% of the combined studies.

Table 4
Percent of Patients Receiving General Anesthesia with Clinical Adverse Experiences (Incidence ≥3%)

	Aprepitant 40 mg (N = 564)	Ondansetron (N = 538)
Infections and Infestations		
Urinary Tract Infection	2.3	3.2
Blood and Lymphatic System Disorders		
Anemia	3.0	4.3
Psychiatric Disorders		
Insomnia	2.1	3.3
Nervous System Disorders		
Headache	5.0	6.5
Cardiac Disorders		
Bradycardia	4.4	3.9
Vascular Disorders		
Hypotension	5.7	4.6
Hypertension	2.1	3.2
Gastrointestinal Disorders		
Nausea	8.5	8.6
Constipation	8.5	7.6
Flatulence	4.1	5.8
Vomiting	2.5	3.9
Skin and Subcutaneous Tissue Disorders		
Pruritus	7.6	8.4
General Disorders and General Administration Site Conditions		
Pyrexia	5.9	10.6

The following additional clinical adverse experiences (incidence >0.5% and greater than ondansetron), regardless of causality, were reported in patients treated with aprepitant:
Infections and infestations: postoperative infection
Metabolism and nutrition disorders: hypokalemia, hypovolemia.
Nervous system disorders: dizziness, hypoesthesia, syncope.
Vascular disorders: hematoma
Respiratory, thoracic and mediastinal disorders: dyspnea, hypoxia, respiratory depression.
Gastrointestinal disorders: abdominal pain, abdominal pain upper, dry mouth, dyspepsia.
Skin and subcutaneous tissue disorders: urticaria
General disorders and administrative site conditions: hypothermia, pain.
Investigations: blood pressure decreased
Injury, poisoning and procedural complications: operative hemorrhage, wound dehiscence.

Other adverse experiences (incidence ≤0.5%) reported in patients treated with aprepitant 40 mg for postoperative nausea and vomiting included:
Nervous system disorders: dysarthria, sensory disturbance.
Eye disorders: miosis, visual acuity reduced.
Respiratory, thoracic and mediastinal disorders: wheezing
Gastrointestinal disorders: bowel sounds abnormal, stomach discomfort.

There were no serious adverse drug-related experiences reported in the postoperative nausea and vomiting clinical studies in patients taking 40-mg aprepitant.

Laboratory Adverse Experiences

One laboratory adverse experience, hemoglobin decreased (40-mg aprepitant 3.8%, ondansetron 4.2%), was reported at an incidence ≥3% in a patient receiving general anesthesia.

The following additional laboratory adverse experiences (incidence >0.5% and greater than ondansetron), regardless of causality, were reported in patients treated with aprepitant 40 mg: blood albumin decreased, blood bilirubin increased, blood glucose increased, blood potassium decreased, glucose urine present.

The adverse experience of ALT increased occurred with similar incidence in patients treated with aprepitant 40 mg (1.1%) as in patients treated with ondansetron 4 mg (1.0%).

Other Studies

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

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

6.2 Postmarketing Experience

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

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

Immune system disorders: hypersensitivity reactions including anaphylactic reactions.

7 DRUG INTERACTIONS

Aprepitant is a substrate, a weak-to-moderate (dose-dependent) inhibitor, and an inducer of CYP3A4. Aprepitant is also an inducer of CYP2C9.

7.1 Effect of Aprepitant on the Pharmacokinetics of Other Agents

CYP3A4 substrates:

Weak inhibition of CYP3A4 by a single 40-mg dose of aprepitant is not expected to alter the plasma concentrations of concomitant medications that are primarily metabolized through CYP3A4 to a clinically significant degree. However, higher aprepitant doses or repeated dosing at any aprepitant dose may have a clinically significant effect.

As a moderate inhibitor of CYP3A4 at a dose of 125 mg/80 mg, aprepitant can increase plasma concentrations of concomitantly administered oral medications that are metabolized through CYP3A4 *[see Contraindications (4)]*. The use of fosaprepitant may increase CYP3A4 substrate plasma concentrations to a lesser degree than the use of oral aprepitant (125 mg).

5-HT_3 antagonists:

In clinical drug interaction studies, aprepitant did not have clinically important effects on the pharmacokinetics of ondansetron, granisetron, or hydrodolasetron (the active metabolite of dolasetron).

Corticosteroids:

Dexamethasone: EMEND, when given as a regimen of 125 mg with dexamethasone coadministered orally as 20 mg on Day 1, and EMEND when given as 80 mg/day with dexamethasone coadministered orally as 8 mg on Days 2 through 5, increased the AUC of dexamethasone, a CYP3A4 substrate, by 2.2-fold on Days 1 and 5. The oral dexamethasone doses should be reduced by approximately 50% when coadministered with EMEND (125-mg/80-mg regimen), to achieve exposures of dexamethasone similar to those obtained when it is given without EMEND. The daily dose of dexamethasone administered in clinical chemotherapy induced nausea and vomiting studies with EMEND reflects an approximate 50% reduction of the dose of dexamethasone *[see Dosage and Administration (2.1)]*. A single dose of EMEND (40 mg) when coadministered with a single oral dose of dexamethasone 20 mg, increased the AUC of dexamethasone by 1.45-fold. Therefore, no dose adjustment is recommended.

Methylprednisolone: EMEND, when given as a regimen of 125 mg on Day 1 and 80 mg/day on Days 2 and 3, increased the AUC of methylprednisolone, a CYP3A4 substrate, by 1.34-fold on Day 1 and by 2.5-fold on Day 3, when methylprednisolone was coadministered intravenously as 125 mg on Day 1 and orally as 40 mg on Days 2 and 3. The IV methylprednisolone dose should be reduced by approximately 25%, and the oral methylprednisolone dose should be reduced by approximately 50% when coadministered with EMEND (125-mg/80-mg regimen) to achieve exposures of methylprednisolone similar to those obtained when it is given without EMEND. Although the concomitant administration of methylprednisolone with the single 40-mg dose of aprepitant 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. Therefore, no dose adjustment is recommended.

Chemotherapeutic agents: *[see Warnings and Precautions (5.1)]*

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.

CYP2C9 substrates (Warfarin, Tolbutamide):

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

Warfarin: A single 125-mg dose of EMEND was administered on Day 1 and 80 mg/day on Days 2 and 3 to healthy subjects who were stabilized on chronic warfarin therapy. Although there was no effect of EMEND on the plasma AUC of R(+) or S(-) warfarin determined on Day 3, there was a 34% decrease in S(-) warfarin (a CYP2C9 substrate) trough concentration accompanied by a 14% decrease in the prothrombin time (reported as International Normalized Ratio or INR) 5 days after completion of dosing with EMEND. In patients on chronic warfarin therapy, the prothrombin time (INR) should be closely monitored in the 2-week period, particularly at 7 to 10 days, following initiation of the 3-day regimen 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.

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

EMEND, when given as a 40-mg single oral dose on Day 1, decreased the AUC of tolbutamide (a CYP2C9 substrate) 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 orally prior to the administration of EMEND 40 mg and on Days 2, 4, 8, and 15. This effect was not considered clinically important.

Oral contraceptives:

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

In another study, a daily dose of an oral contraceptive containing ethinyl estradiol and norethindrone was administered on Days 1 through 21, and EMEND was given as a 3-day regimen of 125 mg on Day 8 and 80 mg/day on Days 9 and 10 with ondansetron 32 mg IV on Day 8 and oral dexamethasone given as 12 mg on Day 8 and 8 mg/day on Days 9, 10, and 11. In the study, the AUC of ethinyl estradiol decreased by 19% on Day 10 and there was as much as a 64% decrease in ethinyl estradiol trough concentrations during Days 9 through 21. While there was no effect of EMEND on the AUC of norethindrone on Day 10, there was as much as a 60% decrease in norethindrone trough concentrations during Days 9 through 21.

In another study, a daily dose of an oral contraceptive containing ethinyl estradiol and norgestimate (which is converted to norelgestromin) was administered on Days 1 through 21, and EMEND 40 mg was given on Day 8. In the study, the AUC of ethinyl estradiol decreased by 4% and 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.

The coadministration of EMEND may reduce the efficacy of hormonal contraceptives (these can include birth control pills, skin patches, implants, and certain IUDs) during and for 28 days after administration of the last dose of EMEND. Alternative or back-up methods of contraception should be used during treatment with EMEND and for 1 month following the last dose of EMEND.

Midazolam:

EMEND increased the AUC of midazolam, a sensitive CYP3A4 substrate, by 2.3-fold on Day 1 and 3.3-fold on Day 5, when a single oral dose of midazolam 2 mg was coadministered on Day 1 and Day 5 of a regimen of EMEND 125 mg on Day 1 and 80 mg/day on Days 2 through 5. The potential effects of increased plasma concentrations of midazolam or other benzodiazepines metabolized via CYP3A4 (alprazolam, triazolam) should be considered when coadministering these agents with EMEND (125 mg/80 mg). A single dose of EMEND (40 mg) increased the AUC of midazolam by 1.2-fold on Day 1, when a single oral dose of midazolam 2 mg was coadministered on Day 1 with EMEND 40 mg; this effect was not considered clinically important.

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

An additional study was completed with intravenous administration of midazolam and EMEND. Intravenous midazolam 2 mg was given 1 hour after oral administration of a single dose of EMEND 125 mg. The plasma AUC of midazolam was increased by 1.5-fold. Depending on clinical situations (e.g., elderly patients) and degree of monitoring available, dosage adjustment for intravenous midazolam may be necessary when it is coadministered with EMEND for the chemotherapy induced nausea and vomiting indication (125 mg on Day 1 followed by 80 mg on Days 2 and 3).

7.2 Effect of Other Agents on the Pharmacokinetics of Aprepitant

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

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

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

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

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

7.3 Additional Interactions

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.

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

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic effects

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

8.3 Nursing Mothers

Aprepitant is excreted in the milk of rats. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for possible serious adverse reactions in nursing infants from aprepitant and because of the potential for tumorigenicity shown for aprepitant in rodent carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

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

8.5 Geriatric Use

In 2 well-controlled chemotherapy-induced nausea and vomiting clinical studies, of the total number of patients (N=544) treated with EMEND, 31% were 65 and over, while 5% were 75 and over. In well-controlled postoperative nausea and vomiting clinical studies, of the total number of patients (N=1120) treated with EMEND, 7% were 65 and over, while 2% were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Greater sensitivity of some older individuals cannot be ruled out. Dosage adjustment in the elderly is not necessary.

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 aprepitant.

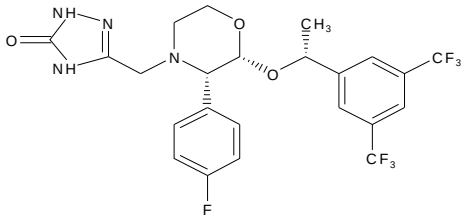
In the event of overdose, EMEND should be discontinued and general supportive treatment and monitoring should be provided. Because of the antiemetic activity of aprepitant, drug-induced emesis may not be effective.

Aprepitant cannot be removed by hemodialysis.

11 DESCRIPTION

EMEND (aprepitant) is a substance P/neurokinin 1 (NK_1) receptor antagonist, chemically described as 5-[[(2*R*,3*S*)-2-[(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro-3*H*-1,2,4-triazol-3-one.

Its empirical formula is $C_{23}H_{21}F_7N_4O_3$, 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.

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 aprepitant doses of 10 mg (N=2), 30 mg (N=3), 100 mg (N=3) or 300 mg (N=5) once daily 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 aprepitant regimen for CINV produces mean trough plasma aprepitant concentrations >500 ng/mL, which would be expected to, based on the fitted curve with the Hill equation, result in >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 aprepitant 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. QT prolongation with the oral dosing regimens for CINV and PONV are 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 80-125 mg, the mean absolute oral bioavailability of aprepitant 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 are non-linear across the clinical dose range. In healthy young adults, the increase in $AUC_{0-\infty}$ was 26% greater than dose proportional between 80-mg and 125-mg single doses administered in the fed state.

Distribution

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

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

Metabolism

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

Excretion

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

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

Specific Populations

Gender

Following oral administration of a single dose of EMEND, the AUC_{0-24hr} and C_{max} are 14% and 22% higher in females as compared with males. The half-life of aprepitant is 25% lower in females as compared with males and T_{max} occurs at approximately the same time. These differences are not considered clinically meaningful. No dosage adjustment is necessary based on gender.

Geriatric

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

Race

Following oral administration of a single dose of EMEND, the $AUC_{0\text{-}24hr}$ and C_{max} are approximately 42% and 29% higher in Hispanics as compared with Caucasians. The $AUC_{0\text{-}24hr}$ and C_{max} are 62% and 41% 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. No dosage adjustment is necessary based on race.

Body Mass Index (BMI)

For every 5 kg/m^2 increase in BMI, $AUC_{0\text{-}24hr}$ and C_{max} of aprepitant decrease by 11%. BMI of subjects in the analysis ranged from 18 kg/m^2 to 36 kg/m^2. This change is not considered clinically meaningful. No dosage adjustment is necessary based on BMI.

Hepatic Insufficiency

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

There are no clinical or pharmacokinetic data in patients with severe hepatic impairment (Child-Pugh score >9) *[see Warnings and Precautions (5.4)].*

Renal Insufficiency

A single 240-mg dose of EMEND was administered to patients with severe renal impairment (creatinine clearance <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 $AUC_{0\text{-}\infty}$ of total aprepitant (unbound and protein bound) decreased by 21% and C_{max} decreased by 32%, relative to healthy subjects (creatinine clearance >80 mL/min estimated by Cockcroft-Gault method). In patients with ESRD undergoing hemodialysis, the $AUC_{0\text{-}\infty}$ 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.

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

treated with oral doses ranging from 2.5 to 2000 mg/kg/day. The highest dose produced a systemic exposure of about 2.8 to 3.6 times the human exposure at the recommended dose. Treatment with aprepitant produced skin fibrosarcomas at 125 and 500 mg/kg/day doses in male mice.

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

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

14 CLINICAL STUDIES

14.1 Prevention of Chemotherapy Induced Nausea and Vomiting (CINV)

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

Highly Emetogenic Chemotherapy (HEC)

In 2 multicenter, randomized, parallel, double-blind, controlled clinical studies, the aprepitant regimen (see Table 6) was compared with standard therapy in patients receiving a chemotherapy regimen that included cisplatin >50 mg/m^2 (mean cisplatin dose = 80.2 mg/m^2). Of the 550 patients who were randomized to receive the aprepitant regimen, 42% were women, 58% men, 59% White, 3% Asian, 5% Black, 12% Hispanic American, and 21% Multi-Racial. The aprepitant-treated patients in these clinical studies ranged from 14 to 84 years of age, with a mean age of 56 years. 170 patients were 65 years or older, with 29 patients being 75 years or older.

Patients (N = 1105) were randomized to either the aprepitant regimen (N = 550) or standard therapy (N = 555). The treatment regimens are defined in Table 5.

Table 5: Treatment Regimens in

Highly Emetogenic Chemotherapy Trials*

Treatment Regimen	Day 1	Days 2 to 4
Aprepitant	Aprepitant 125 mg PO Dexamethasone 12 mg PO 5-HT$_3$ antagonist†	Aprepitant 80 mg PO Daily (Days 2 and 3 only) Dexamethasone 8 mg PO Daily (morning)
Standard Therapy	Dexamethasone 20 mg PO 5-HT$_3$ antagonist†	Dexamethasone 8 mg PO Daily (morning) Dexamethasone 8 mg PO Daily (evening)

*Aprepitant placebo and dexamethasone placebo were used to maintain blinding.

†Ondansetron 32 mg I.V. 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 package insert for the current dosing.

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

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

Primary endpoint:

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

Other prespecified endpoints:

- complete protection (defined as no emetic episodes, no use of rescue therapy, and a maximum nausea visual analogue scale [VAS] score <25 mm on a 0 to 100 mm scale)
- no emesis (defined as no emetic episodes regardless of use of rescue therapy)
- no nausea (maximum VAS <5 mm on a 0 to 100 mm scale)
- no significant nausea (maximum VAS <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 6 and in Table 7.

Table 6
Percent of Patients Receiving Highly Emetogenic Chemotherapy Responding by Treatment Group and Phase for Study 1 — Cycle 1

ENDPOINTS	Aprepitant Regimen (N = 260)[†] %	Standard Therapy (N = 261)[†] %	p-Value
PRIMARY ENDPOINT			
Complete Response			
Overall[‡]	73	52	<0.001
OTHER PRESPECIFIED ENDPOINTS			
Complete Response			
Acute phase[§]	89	78	<0.001
Delayed phase[‖]	75	56	<0.001
Complete Protection			
Overall	63	49	0.001
Acute phase	85	75	NS*
Delayed phase	66	52	<0.001
No Emesis			
Overall	78	55	<0.001
Acute phase	90	79	0.001
Delayed phase	81	59	<0.001
No Nausea			
Overall	48	44	NS**
Delayed phase	51	48	NS**
No Significant Nausea			
Overall	73	66	NS**
Delayed phase	75	69	NS**

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

Table 7

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

ENDPOINTS	Aprepitant Regimen (N = 261)[†] %	Standard Therapy (N = 263)[†] %	p-Value
PRIMARY ENDPOINT			

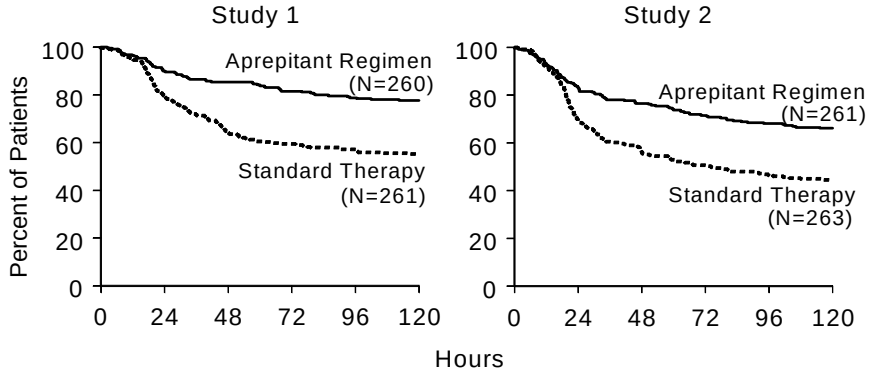
Complete Response			
Overall[‡]	63	43	<0.001
OTHER PRESPECIFIED ENDPOINTS			
Complete Response			
Acute phase[§]	83	68	<0.001
Delayed phase[‖]	68	47	<0.001
Complete Protection			
Overall	56	41	<0.001
Acute phase	80	65	<0.001
Delayed phase	61	44	<0.001
No Emesis			
Overall	66	44	<0.001
Acute phase	84	69	<0.001
Delayed phase	72	48	<0.001
No Nausea			
Overall	49	39	NS*
Delayed phase	53	40	NS*
No Significant Nausea			
Overall	71	64	NS**
Delayed phase	73	65	NS**

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

In both studies, a statistically significantly higher proportion of patients receiving the aprepitant 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 aprepitant regimen was also observed when the acute phase and the delayed phase were analyzed separately.

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

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



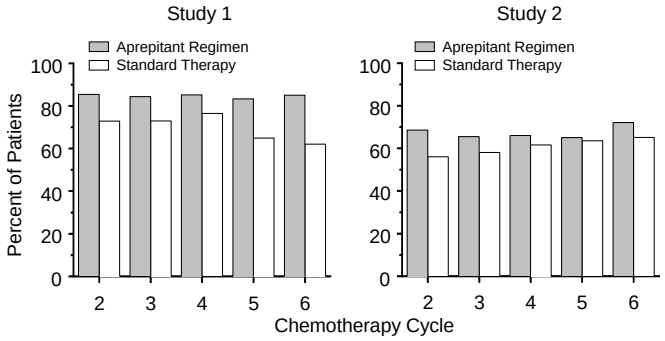
p-Value <0.001 based on a log rank test for Study 1 and Study 2; nominal p-values not adjusted for multiplicity.

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

of patients receiving the aprepitant regimen reported minimal or no impact of nausea and vomiting on daily life (Study 1: 74% versus 64%; Study 2: 75% versus 64%).

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

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



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

Moderately Emetogenic Chemotherapy (MEC)

In a multicenter, randomized, double-blind, parallel-group, clinical study in breast cancer patients, the aprepitant regimen (see Table 9) was compared with a standard of care therapy in patients receiving a moderately emetogenic chemotherapy regimen that included cyclophosphamide 750-1500 mg/m^2; or cyclophosphamide 500-1500 mg/m^2 and doxorubicin (≤60 mg/m^2) or epirubicin (≤100 mg/m^2).

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

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

Patients (N = 866) were randomized to either the aprepitant regimen (N = 438) or standard therapy (N = 428). The treatment regimens are defined in Table 8.

Table 8: Treatment Regimens in Moderately Emetogenic Chemotherapy Trials

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

Aprepitant placebo and dexamethasone placebo were used to maintain blinding.
[†]1 hour prior to chemotherapy.
[‡]30 minutes prior to chemotherapy.
[§]30 to 60 minutes prior to chemotherapy and 8 hours after first ondansetron dose.

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

Primary endpoint:

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

Other prespecified endpoints:

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

A summary of the key results from this study is shown in Table 9.

Table 9
Percent of Patients Receiving Moderately Emetogenic Chemotherapy Responding by Treatment Group and Phase — Cycle 1

ENDPOINTS	Aprepitant 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.

In this study, a statistically significantly (p=0.015) higher proportion of patients receiving the aprepitant regimen (51%) in Cycle 1 had a complete response (primary endpoint) during the overall phase compared with patients receiving standard therapy (42%). The difference between treatment groups was primarily driven by the “No Emesis Endpoint”, a principal component of this composite primary endpoint. In addition, a higher proportion of patients receiving the aprepitant regimen in Cycle 1 had a complete response during the acute (0-24 hours) and delayed (25-120 hours) phases compared with patients receiving standard therapy; however, the treatment group differences failed to reach statistical significance, after multiplicity adjustments.

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

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

Postmarketing Trial: In a postmarketing, multicenter, randomized, double-blind, parallel-group, clinical study in 848 cancer patients, the aprepitant regimen (N=430) was compared with a standard of care therapy (N=418) in patients receiving a moderately emetogenic chemotherapy regimen that included any

IV dose of oxaliplatin, carboplatin, epirubicin, idarubicin, ifosfamide, irinotecan, daunorubicin, doxorubicin; cyclophosphamide IV (<1500 mg/m^2); or cytarabine IV (>1 g/m^2).

Of the 430 patients who were randomized to receive the aprepitant 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 aprepitant-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. Patients receiving the aprepitant 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.

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 this study is shown in Table 10.

Table 10
Percent of Patients Receiving Moderately Emetogenic Chemotherapy Responding by Treatment Group for Study 2 — Cycle 1

ENDPOINTS	Aprepitant 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.

In this study, a statistically significantly higher proportion of patients receiving the aprepitant 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 aprepitant 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 aprepitant 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 aprepitant 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 aprepitant were observed to have no vomiting and complete response compared to patients receiving standard therapy. For gender, the difference in complete response rates between the aprepitant 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 gender was observed for the no vomiting endpoint.

14.2 Prevention of Postoperative Nausea and Vomiting (PONV)

In two multicenter, randomized, double-blind, active comparator-controlled, parallel-group clinical studies (PONV Studies 1 and 2), aprepitant was compared with ondansetron for the prevention of postoperative nausea and vomiting in 1658 patients undergoing open abdominal surgery. Patients were randomized to receive 40-mg aprepitant, 125-mg aprepitant, or 4-mg ondansetron. Aprepitant 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 125-mg dose and the 40-mg dose did not demonstrate any additional clinical benefit. The remainder of this section will focus on the results in the 40-mg aprepitant dose recommended for PONV.

Of the 564 patients who received 40-mg aprepitant, 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 aprepitant 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. The two pivotal studies were of similar design; however, they differed in terms of study hypothesis, efficacy analyses and geographic location. PONV Study 1 was a multinational study including the U.S., whereas, PONV Study 2 was conducted entirely in the U.S.

Efficacy measures in PONV Study 1 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 aprepitant and 4-mg ondansetron are described in Table 11:

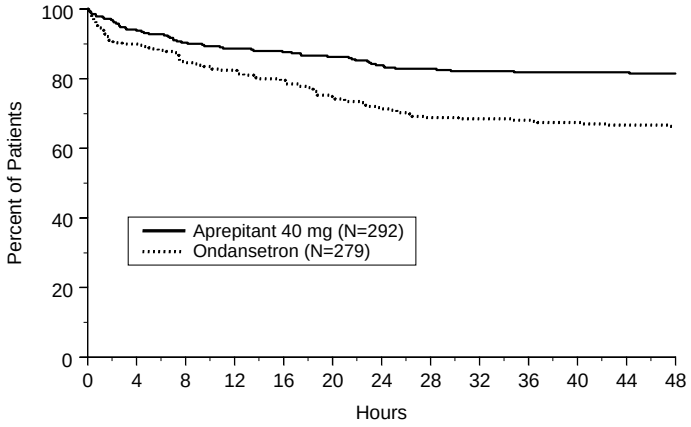
Table 11
PONV Study 1
Response Rates for Select Efficacy Endpoints
(Modified-Intention-to-Treat Population)

Treatment	n/m (%)	Aprepitant vs Ondansetron		
		Δ	Odds ratio†	Analysis
Primary Endpoints				
No Vomiting 0 to 24 hours (Superiority) (no emetic episodes)				
Aprepitant 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)				
Aprepitant 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)				
Aprepitant 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)				
Aprepitant 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 (%): Aprepitant 40 mg minus Ondansetron.
‡ LB= lower bound of 1-sided 97.5% confidence interval for the odds ratio.
* P-value of two-sided test <0.05.
+ Based on the prespecified fixed sequence multiplicity strategy, Aprepitant 40 mg was not superior to Ondansetron.
† Estimated odds ratio for Aprepitant versus Ondansetron. A value of >1 favors Aprepitant over Ondansetron.

The use of aprepitant did not affect the time to first use of rescue medication when compared to ondansetron. However, compared to the ondansetron group, use of aprepitant 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



Efficacy measures in PONV Study 2 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).

PONV Study 2 failed to satisfy its primary hypothesis that aprepitant 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 both dose levels of aprepitant had a clinically meaningful effect with respect to the secondary endpoint “no vomiting” during the first 24 hours after surgery and showed that the use of 40-mg aprepitant was associated with a 16% improvement over ondansetron for the no vomiting endpoint.

Table 12
PONV Study 2
(Modified-Intention-to-Treat Population)

Treatment	n/m (%)	Aprepitant vs Ondansetron		
		Δ	Odds ratio†	p-Value
Primary Endpoint				
Complete Response (no emesis and no rescue therapy, 0 to 24 hours)				
Aprepitant 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)				
Aprepitant 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)				

Aprepitant 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)				
Aprepitant 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 (%): Aprepitant 40 mg minus Ondansetron. † Estimated odds ratio: Aprepitant 40 mg versus Ondansetron. * Not statistically significant after pre-specified multiplicity adjustment.				

16 HOW SUPPLIED/STORAGE AND HANDLING

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. 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. 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.

Storage

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

17 PATIENT COUNSELING INFORMATION

"See FDA-Approved Patient Labeling (Patient Information)"

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

Patients should be instructed to take EMEND only as prescribed. For the prevention of chemotherapy induced nausea and vomiting (CINV), patients should be advised to take their first dose (125 mg) of EMEND 1 hour prior to chemotherapy treatment. For the prevention of postoperative nausea and vomiting (PONV), patients should receive their medication (40-mg capsule of EMEND) within 3 hours prior to induction of anesthesia.

Allergic reactions, which may be serious, and may include hives, rash and itching and cause difficulty in breathing or swallowing, have been reported in general use with EMEND. Physicians should instruct their patients to stop taking EMEND and call their doctor right away if they experience an allergic reaction. In addition, severe skin reactions may occur rarely.

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

Patients on chronic warfarin therapy should be instructed to have their clotting status closely monitored in the 2-week period, particularly at 7 to 10 days, following initiation of the 3-day regimen of EMEND 125 mg/80 mg with each chemotherapy cycle, or following administration of a single 40-mg dose of EMEND for the prevention of postoperative nausea and vomiting.

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

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

U.S. Patent Nos.: 5,719,147; 6,096,742

USPI-C-08691212R005

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

EMEND (fosaprepitant dimeglumine) for Injection, for intravenous use
Initial U.S. Approval: 2008

----------INDICATIONS AND USAGE ----------
EMEND® for Injection is a substance P/neurokinin-1 (NK_1) receptor antagonist, in combination with other antiemetic agents, is indicated in adults for the (1):
- prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including high-dose cisplatin
- prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC)

Limitations of Use (1)
- Chronic continuous administration is not recommended.

---------- DOSAGE AND ADMINISTRATION----------
- *HEC (Single Dose Regimen):* EMEND for Injection (150 mg) is administered on Day 1 only as an infusion **over 20-30 minutes** initiated approximately 30 minutes prior to chemotherapy. No capsules of EMEND are administered on Days 2 and 3. EMEND for Injection is part of a regimen to prevent nausea and vomiting induced by HEC that includes a corticosteroid and a 5-HT_3 antagonist. (2.1)
- *HEC and MEC (3-Day Dosing Regimen):* EMEND for Injection (115 mg) is administered on Day 1 as an infusion **over 15 minutes** initiated approximately 30 minutes prior to chemotherapy. EMEND capsules (80 mg) are given orally on Days 2 and 3. EMEND for Injection and EMEND capsules are part of a regimen to prevent nausea and vomiting induced by HEC or MEC that includes a corticosteroid and a 5-HT_3 antagonist. (2.1, 2.2)

---------- DOSAGE FORMS AND STRENGTHS ----------
One single dose glass vial supplied as sterile lyophilized powder for intravenous use only after reconstitution and dilution: 150 mg and 115 mg (3)

----------CONTRAINDICATIONS ----------
- Known hypersensitivity to any component of this drug. (4)
- Do not use concurrently with pimozide or cisapride, since inhibition of CYP3A4 by aprepitant may result in elevated plasma concentrations of these drugs, potentially causing serious or life-threatening reactions. (4)

----------WARNINGS AND PRECAUTIONS----------
- Fosaprepitant should be used with caution in patients receiving concomitant medications that are primarily metabolized through CYP3A4. (5.1)
- Immediate hypersensitivity reactions may occur during infusion. Patients have generally responded to discontinuation. It is not recommended to reinitiate the infusion. (5.2)
- Coadministration of fosaprepitant or aprepitant with warfarin (a CYP2C9 substrate) may result in a clinically significant decrease in International Normalized Ratio (INR) of prothrombin time. (5.3)
- The efficacy of hormonal contraceptives during and for 28 days following the last dose of fosaprepitant or aprepitant may be reduced. Alternative or back-up methods of contraception should be used. (5.4)

---------- ADVERSE REACTIONS----------
- Adverse reactions for the CINV oral aprepitant regimen in conjunction with highly and moderately emetogenic chemotherapy (incidence ≥1% and greater than standard therapy) are: hiccups, asthenia/fatigue, AST/ALT increased, headache, constipation, anorexia, dyspepsia, diarrhea, eructation. (6.1)
- Adverse reactions reported for EMEND for Injection were generally similar to that seen in prior HEC studies with oral aprepitant. In addition, infusion site reactions (3%) occurred with EMEND for Injection. (6.1)

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 ----------
- Coadministration of fosaprepitant or aprepitant with drugs that inhibit or induce CYP3A4 activity may result in increased or reduced plasma concentrations of aprepitant, respectively. (7.1, 7.2)
- Coadministration of EMEND for Injection with drugs that are metabolized by CYP2C9 (e.g., warfarin, tolbutamide), may result in lower plasma concentrations of these drugs. (7.1)

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

Revised: 12/2012

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

EMEND® for Injection is a substance P/neurokinin-1 (NK_1) receptor antagonist indicated in adults for use in combination with other antiemetic agents 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 *[see Dosage and Administration (2.1)]*
- prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC) *[see Dosage and Administration (2.2)]*.

Limitations of Use

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

Chronic continuous administration is not recommended *[see Warnings and Precautions (5.5)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Prevention of Nausea and Vomiting Associated with Highly Emetogenic Chemotherapy (HEC)

EMEND for Injection 150 mg (Single Dose Regimen of EMEND):

EMEND for Injection 150 mg is administered intravenously on Day 1 only as an infusion **over 20-30 minutes** initiated approximately 30 minutes prior to chemotherapy. No capsules of EMEND are administered on Days 2 and 3. EMEND for Injection should be administered in conjunction with a corticosteroid and a 5-HT_3 antagonist as specified in Table 1. The recommended dosage of dexamethasone with EMEND for Injection 150 mg differs from the recommended dosage of dexamethasone with EMEND for Injection 115 mg on Days 3 and 4. The package insert for the co-administered 5-HT_3 antagonist must be consulted prior to initiation of treatment with EMEND for Injection.

Table 1
Recommended dosing (Single Dose Regimen of EMEND) for the prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy

	Day 1	Day 2	Day 3	Day 4
EMEND	150 mg intravenous	none	none	none
Dexamethasone*	12 mg orally	8 mg orally	**8 mg orally twice daily**	**8 mg orally twice daily**
5-HT_3 antagonist	See the package insert for the selected 5-HT_3 antagonist for appropriate dosing information.	none	none	none

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

EMEND for Injection 115 mg (3-Day Dosing Regimen of EMEND):

EMEND for Injection 115 mg is administered on Day 1 only as an infusion **over 15 minutes** initiated 30 minutes prior to chemotherapy. Capsules of EMEND 80 mg should be administered on Days 2 and 3. EMEND for Injection 115 mg should be administered in conjunction with a corticosteroid and a 5-HT_3 antagonist as specified in Table 2. The recommended dosage of dexamethasone with EMEND for Injection 115 mg differs from the recommended dosage of dexamethasone with EMEND for Injection 150 mg on Days 3 and 4. The package insert for the co-administered 5-HT_3 antagonist must be consulted prior to initiation of treatment with EMEND for Injection.

Capsules of EMEND 125 mg may be substituted for EMEND for Injection 115 mg on Day 1.

Table 2 Recommended dosing (3-Day Dosing Regimen of EMEND) for the prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy				
	Day 1	Day 2	Day 3	Day 4
EMEND	115 mg intravenous	80 mg orally	80 mg orally	none
Dexamethasone*	12 mg orally	8 mg orally	**8 mg orally once daily**	**8 mg orally once daily**
5-HT_3 antagonist	See the package insert for the selected 5-HT_3 antagonist for appropriate dosing information.	none	none	none

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

2.2 Prevention of Nausea and Vomiting Associated with Moderately Emetogenic Chemotherapy (MEC)

EMEND for Injection 115 mg (3-Day Dosing Regimen of EMEND):

EMEND for Injection 115 mg is administered on Day 1 only as an infusion **over 15 minutes** initiated 30 minutes prior to chemotherapy. Capsules of EMEND 80 mg should be administered on Days 2 and 3. EMEND for Injection 115 mg should be administered in conjunction with a corticosteroid and a 5-HT_3 antagonist as specified in Table 3. The recommended dosage of dexamethasone with EMEND for Injection 115 mg differs from the recommended dosage of dexamethasone with EMEND for Injection 150 mg on Days 3 and 4. The package insert for the co-administered 5-HT_3 antagonist must be consulted prior to initiation of treatment with EMEND for Injection.

Capsules of EMEND 125 mg may be substituted for EMEND for Injection 115 mg on Day 1.

Table 3 Recommended dosing (3-Day Dosing Regimen of EMEND) for the prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy			
	Day 1	Day 2	Day 3
EMEND	115 mg intravenous	80 mg orally	80 mg orally
Dexamethasone*	12 mg orally	none	none
5-HT_3 antagonist	See the package insert for the selected 5-HT_3 antagonist for appropriate dosing information.	none	none

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

2.3 Preparation of EMEND for Injection

Table 4 Preparation Instructions for EMEND for Injection (115 mg and 150 mg)		
	115 mg	***150 mg***
Step 1	Aseptically inject 5 mL 0.9% Sodium Chloride for Injection (normal saline) into the vial. Assure that normal saline is added to the vial along the vial wall in order to prevent foaming. Swirl the vial gently. Avoid shaking and jetting saline into the vial.	Aseptically inject 5 mL 0.9% Sodium Chloride for Injection (normal saline) into the vial. Assure that normal saline is added to the vial along the vial wall in order to prevent foaming. Swirl the vial gently. Avoid shaking and jetting saline into the vial.
Step 2	Aseptically prepare an infusion bag filled with **110 mL** of normal saline.	Aseptically prepare an infusion bag filled with **145 mL** of normal saline.
Step 3	Aseptically withdraw the entire volume from the vial and transfer it into the infusion bag containing **110 mL** of normal saline to yield a total volume of **115 mL** and a final concentration of 1 mg/1 mL.	Aseptically withdraw the entire volume from the vial and transfer it into the infusion bag containing **145 mL** of normal saline to yield a total volume of **150 mL** and a final concentration of 1 mg/1 mL**.**
Step 4	Gently invert the bag 2-3 times.	Gently invert the bag 2-3 times.
	Note: *The differences in preparation for each dose are displayed as bolded text.*	

The reconstituted final drug solution is stable for 24 hours at ambient room temperature (at or below 25°C).

Parenteral drug products should be inspected visually for particulate matter and discoloration before administration whenever solution and container permit.

Caution: EMEND for Injection should not be mixed or reconstituted with solutions for which physical and chemical compatibility have not been established. EMEND for Injection is incompatible with any solutions containing divalent cations (e.g., Ca^{2+}, Mg^{2+}), including Lactated Ringer's Solution and Hartmann's Solution.

3 DOSAGE FORMS AND STRENGTHS

One 150-mg single dose glass vial: White to off-white lyophilized solid (Sterile lyophilized powder for intravenous use only after reconstitution and dilution).

One 115-mg single dose glass vial: White to off-white lyophilized solid (Sterile lyophilized powder for intravenous use only after reconstitution and dilution).

4 CONTRAINDICATIONS

4.1 Hypersensitivity

EMEND for Injection is contraindicated in patients who are hypersensitive to EMEND for Injection, aprepitant, polysorbate 80 or any other components of the product. Known hypersensitivity reactions include: flushing, erythema, dyspnea, and anaphylactic reactions *[see Adverse Reactions (6.2)]*.

4.2 Concomitant Use with Pimozide or Cisapride

Aprepitant, when administered orally, is a moderate cytochrome P450 isoenzyme 3A4 (CYP3A4) inhibitor following the 3-day antiemetic dosing regimen for CINV. Since fosaprepitant is rapidly converted to aprepitant, do not use fosaprepitant concurrently with pimozide or cisapride. Inhibition of CYP3A4 by

aprepitant could result in elevated plasma concentrations of these drugs, potentially causing serious or life-threatening reactions *[see Drug Interactions (7.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 CYP3A4 Interactions

Fosaprepitant is rapidly converted to aprepitant, which is a moderate inhibitor of CYP3A4 when administered as a 3-day antiemetic dosing regimen for CINV. Fosaprepitant should be used with caution in patients receiving concomitant medications that are primarily metabolized through CYP3A4. Inhibition of CYP3A4 by aprepitant or fosaprepitant could result in elevated plasma concentrations of these concomitant medications. When fosaprepitant is used concomitantly with another CYP3A4 inhibitor, aprepitant plasma concentrations could be elevated. When aprepitant is used concomitantly with medications that induce CYP3A4 activity, aprepitant plasma concentrations could be reduced, and this may result in decreased efficacy of aprepitant *[see Drug Interactions (7.1)]*.

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

In separate pharmacokinetic studies, no clinically significant change in docetaxel or vinorelbine pharmacokinetics was observed when the oral aprepitant regimen was coadministered.

Due to the small number of patients in clinical studies who received the CYP3A4 substrates vinblastine, vincristine, or ifosfamide, particular caution and careful monitoring are advised in patients receiving these agents or other chemotherapy agents metabolized primarily by CYP3A4 that were not studied *[see Drug Interactions (7.1)]*.

5.2 Hypersensitivity Reactions

Isolated reports of immediate hypersensitivity reactions including flushing, erythema, dyspnea, and anaphylaxis have occurred during infusion of fosaprepitant. These hypersensitivity reactions have generally responded to discontinuation of the infusion and administration of appropriate therapy. Reinitiation of the infusion is not recommended in patients who experience these symptoms during first-time use.

5.3 Coadministration with Warfarin (a CYP2C9 substrate)

Coadministration of fosaprepitant or aprepitant with warfarin may result in a clinically significant decrease in International Normalized Ratio (INR) of prothrombin time. In patients on chronic warfarin therapy, the INR should be closely monitored in the 2-week period, particularly at 7 to 10 days, following initiation of fosaprepitant with each chemotherapy cycle *[see Drug Interactions (7.1)]*.

5.4 Coadministration with Hormonal Contraceptives

Upon coadministration with fosaprepitant or aprepitant, the efficacy of hormonal contraceptives may be reduced during and for 28 days following the last dose of either fosaprepitant or aprepitant. Alternative or back-up methods of contraception should be used during treatment with and for 1 month following the last dose of fosaprepitant or aprepitant *[see Drug Interactions (7.1)]*.

5.5 Chronic Continuous Use

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

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.

Since EMEND for Injection is converted to aprepitant, those adverse reactions associated with aprepitant might also be expected to occur with EMEND for Injection.

The overall safety of fosaprepitant was evaluated in approximately 1100 individuals and the overall safety of aprepitant was evaluated in approximately 6500 individuals.

Oral Aprepitant

Highly Emetogenic Chemotherapy (HEC)

In 2 well-controlled clinical trials in patients receiving highly emetogenic cancer chemotherapy, 544 patients were treated with aprepitant during Cycle 1 of chemotherapy and 413 of these patients continued into the Multiple-Cycle extension for up to 6 cycles of chemotherapy. Oral aprepitant was given in combination with ondansetron and dexamethasone.

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

The most common adverse reactions reported in patients treated with the aprepitant regimen with an incidence ≥1% and greater than standard therapy are listed in Table 5.

Table 5
Adverse Reactions (incidence ≥1%) in patients receiving HEC with a greater incidence in the Aprepitant Regimen relative to Standard Therapy

	Aprepitant Regimen (N=544)	Standard Therapy (N=550)
Respiratory System		
hiccups	4.6	2.9
Body as a Whole/Site Unspecified		
asthenia/fatigue	2.9	1.6
Investigations		
ALT increased	2.8	1.5
AST increased	1.1	0.9
Digestive System		
constipation	2.2	2.0
dyspepsia	1.5	0.7
diarrhea	1.1	0.9
Nervous System		
headache	2.2	1.8
Metabolism and Nutrition		
anorexia	2.0	0.5

A listing of adverse reactions in the aprepitant regimen (incidence <1%) that occurred at a greater incidence than standard therapy are presented in the *Less Common Adverse Reactions* subsection below.

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

Moderately Emetogenic Chemotherapy (MEC)

In 2 well-controlled clinical trials in patients receiving moderately emetogenic cancer chemotherapy, 868 patients were treated with the aprepitant regimen during Cycle 1 of chemotherapy and 686 of these patients continued into extensions for up to 4 cycles of chemotherapy. In both studies, oral aprepitant was given in combination with ondansetron and dexamethasone (aprepitant regimen).

In the combined analysis of Cycle 1 data for these 2 studies, adverse reactions were reported in approximately 14% of patients treated with the aprepitant regimen compared with approximately 15% of patients treated with standard therapy. Treatment was discontinued due to adverse reactions in 0.7% of patients treated with the aprepitant regimen compared with 0.2% of patients treated with standard therapy.

The most common adverse reactions reported in patients treated with the aprepitant regimen with an incidence ≥1% and greater than standard therapy are listed in Table 6.

Table 6
Adverse Reactions (incidence ≥1%) in patients receiving MEC with a greater incidence in the Aprepitant Regimen relative to Standard Therapy

	Aprepitant Regimen (N=868)	Standard Therapy (N=846)
Gastrointestinal disorders		
eructation	1.0	0.1
General disorders and administration site conditions		
fatigue	1.4	0.9

A listing of adverse reactions in the aprepitant regimen (incidence <1%) that occurred at a greater incidence than standard therapy are presented in the *Less Common Adverse Reactions* subsection below.

Less Common Adverse Reactions

Adverse reactions reported in either HEC or MEC studies in patients treated with the aprepitant regimen with an incidence <1% and greater than standard therapy are listed in Table 7.

Table 7
Adverse Reactions (incidence <1%) in patients observed in either HEC or MEC Studies with a greater incidence in the Aprepitant Regimen relative to Standard Therapy

Infection and infestations	candidiasis, staphylococcal infection
Blood and the lymphatic system disorders	anemia, febrile neutropenia
Metabolism and nutrition disorders	weight gain, polydipsia
Psychiatric disorders	disorientation, euphoria, anxiety
Nervous system disorders	dizziness, dream abnormality, cognitive disorder, lethargy, somnolence
Eye disorders	conjunctivitis
Ear and labyrinth disorders	tinnitus
Cardiac disorders	bradycardia, cardiovascular disorder, palpitations
Vascular disorders	hot flush, flushing
Respiratory, thoracic and mediastinal disorders	pharyngitis, sneezing, cough, postnasal drip, throat irritation
Gastrointestinal disorders	nausea, acid reflux, dysgeusia, epigastric discomfort, obstipation, gastroesophageal reflux disease, perforating duodenal ulcer, vomiting, abdominal pain, dry mouth, abdominal distension, faeces hard, neutropenic colitis, flatulence, stomatitis
Skin and subcutaneous tissue disorders	rash, acne, photosensitivity, hyperhidrosis, oily skin, pruritus, skin lesion
Musculoskeletal and connective tissue disorders	muscle cramp, myalgia, muscular weakness
Renal and urinary disorders	polyuria, dysuria, pollakiuria
General disorders and administration site condition	edema, chest discomfort, malaise, thirst, chills, gait disturbance
Investigations	alkaline phosphatase increased, hyperglycemia, microscopic hematuria, hyponatremia, weight decreased, neutrophil count decreased

In another chemotherapy induced nausea and vomiting (CINV) study, Stevens-Johnson syndrome was reported as a serious adverse reaction in a patient receiving aprepitant with cancer chemotherapy.

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

Fosaprepitant

In an active-controlled clinical study in patients receiving highly emetogenic chemotherapy, safety was evaluated for 1143 patients receiving the 1-day regimen of EMEND for Injection 150 mg compared to 1169 patients receiving the 3-day regimen of EMEND (aprepitant). The safety profile was generally similar to that seen in prior HEC studies with aprepitant. However, infusion-site reactions occurred at a higher incidence in patients in the fosaprepitant group (3.0%) compared to those in the aprepitant group (0.5%). The reported infusion-site reactions included infusion-site erythema, infusion-site pruritus, infusion-site pain, infusion-site induration, and infusion-site thrombophlebitis.

The following additional adverse reactions occurred with fosaprepitant 150 mg and were not reported with the oral aprepitant regimen in the corresponding section above.

Table 8
Adverse Reactions (incidence >0.1%) in patients receiving Fosaprepitant 150 mg and not reported above for the Oral Aprepitant Regimen

General disorders and administration site conditions	infusion site erythema, infusion site pruritus, infusion site induration, infusion site pain
Investigations	blood pressure increased
Skin and subcutaneous tissue disorders	erythema
Vascular disorders	thrombophlebitis (predominantly, infusion-site thrombophlebitis)

Other Studies with Postoperative Nausea and Vomiting

In well-controlled clinical studies in patients receiving general balanced anesthesia, 564 patients were administered 40-mg aprepitant orally and 538 patients were administered 4-mg ondansetron intravenously.

Adverse reactions were reported in approximately 4% of patients treated with 40-mg aprepitant compared with approximately 6% of patients treated with 4-mg ondansetron intravenously.

In patients treated with aprepitant, increased ALT (1.1%) was seen at a greater incidence than with ondansetron (1.0%). The following additional adverse reactions were observed in patients treated with aprepitant at an incidence <1% and greater than with ondansetron.

Table 9
Adverse Reactions (incidence <1%) in patients receiving Aprepitant 40 mg with a greater incidence in the Aprepitant group relative to ondansetron

Psychiatric disorders	insomnia
Nervous system disorders	dysarthria, hypoesthesia, sensory disturbance
Eye disorders	miosis, visual acuity reduced
Cardiac disorders	bradycardia
Respiratory, thoracic and mediastinal disorders	dyspnea, wheezing
Gastrointestinal disorders	abdominal pain upper, bowel sounds abnormal, dry mouth, nausea, stomach discomfort

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

Other Studies

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

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of fosaprepitant and aprepitant. 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, rarely Stevens-Johnson syndrome/toxic epidermal necrolysis.

Immune system disorders: hypersensitivity reactions including anaphylactic reactions.

7 DRUG INTERACTIONS

Drug interactions following administration of fosaprepitant are likely to occur with drugs that interact with oral aprepitant.

Aprepitant is a substrate, a moderate inhibitor, and an inducer of CYP3A4 when administered as a 3-day antiemetic dosing regimen for CINV. Aprepitant is also an inducer of CYP2C9.

Fosaprepitant 150 mg, given as a single dose, is a weak inhibitor of CYP3A4, and does not induce CYP3A4. Fosaprepitant or aprepitant is unlikely to interact with drugs that are substrates for the P-glycoprotein transporter.

The following information was derived from data with oral aprepitant, two studies conducted with fosaprepitant and oral midazolam, and one study conducted with fosaprepitant and dexamethasone.

7.1 Effect of Fosaprepitant/Aprepitant on the Pharmacokinetics of Other Agents

CYP3A4 substrates:

Aprepitant, as a moderate inhibitor of CYP3A4, and fosaprepitant 150 mg, as a weak inhibitor of CYP3A4, can increase plasma concentrations of concomitantly coadministered oral medications that are metabolized through CYP3A4 *[see Contraindications (4)]*.

5-HT_3 antagonists:

In clinical drug interaction studies, aprepitant did not have clinically important effects on the pharmacokinetics of ondansetron, granisetron, or hydrodolasetron (the active metabolite of dolasetron).

Corticosteroids:

Dexamethasone: Fosaprepitant 150 mg administered as a single intravenous dose on Day 1 increased the $AUC_{0\text{-}24hr}$ of dexamethasone, administered as a single 8-mg oral dose on Days 1, 2, and 3, by approximately 2-fold on Days 1 and 2. The oral dexamethasone dose on Days 1 and 2 should be reduced by approximately 50% when coadministered with fosaprepitant 150-mg intravenous on Day 1.

An oral aprepitant regimen of 125 mg on Day 1, and 80 mg/day on Days 2 through 5, coadministered with 20-mg oral dexamethasone on Day 1 and 8-mg oral dexamethasone on Days 2 through 5, increased the AUC of dexamethasone by 2.2-fold on Days 1 and 5. The oral dexamethasone doses should be reduced by approximately 50% when coadministered with a regimen of fosaprepitant 115 mg followed by aprepitant.

Methylprednisolone: An oral aprepitant 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. The intravenous methylprednisolone dose should be reduced by approximately 25%, and the oral methylprednisolone dose should be reduced by approximately 50% when coadministered with a regimen of fosaprepitant 115 mg followed by aprepitant.

Chemotherapeutic agents:

Docetaxel: In a pharmacokinetic study, oral aprepitant (CINV regimen) did not influence the pharmacokinetics of docetaxel *[see Warnings and Precautions (5.1)]*.

Vinorelbine: In a pharmacokinetic study, oral aprepitant (CINV regimen) did not influence the pharmacokinetics of vinorelbine to a clinically significant degree *[see Warnings and Precautions (5.1)]*.

Oral contraceptives:

When oral aprepitant, ondansetron, and dexamethasone were 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.

The coadministration of fosaprepitant or aprepitant may reduce the efficacy of hormonal contraceptives (these can include birth control pills, skin patches, implants, and certain IUDs) during and for 28 days after administration of the last dose of fosaprepitant or aprepitant. Alternative or back-up methods of contraception should be used during treatment with and for 1 month following the last dose of fosaprepitant or aprepitant.

Midazolam:

Interactions between aprepitant or fosaprepitant and coadministered midazolam are listed in the table below (increase is indicated as "↑", decrease as "↓", no change as "↔").

Table 10
Pharmacokinetic Interaction Data for Fosaprepitant/Aprepitant and Coadministered Midazolam

Dose of fosaprepitant/ aprepitant	Dose of Midazolam	Observed Drug Interactions
fosaprepitant 150 mg on Day 1	oral 2 mg on Days 1 and 4	AUC ↑ 1.8-fold on Day 1 and AUC ↔ on Day 4
fosaprepitant 100 mg on Day 1	oral 2 mg	oral midazolam AUC ↑ 1.6-fold
oral aprepitant 125 mg on Day 1 and 80 mg on Days 2 to 5	oral 2 mg SD on Days 1 and 5	oral midazolam AUC ↑ 2.3-fold on Day 1 and ↑ 3.3-fold on Day 5
oral aprepitant 125 mg on Day 1 and 80 mg on Days 2 and 3	intravenous 2 mg prior to 3-day regimen of aprepitant and on Days 4, 8 and 15	intravenous midazolam AUC ↑ 25% on Day 4, AUC ↓ 19% on Day 8 and AUC ↓ 4% on Day 15
oral aprepitant 125 mg	intravenous 2 mg given 1 hour after aprepitant	intravenous midazolam AUC ↑ 1.5-fold

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

The potential effects of increased plasma concentrations of midazolam or other benzodiazepines metabolized via CYP3A4 (alprazolam, triazolam) should be considered when coadministering these agents with fosaprepitant or aprepitant.

CYP2C9 substrates (Warfarin, Tolbutamide):

Warfarin: A single 125-mg dose of oral aprepitant 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 oral aprepitant 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 oral aprepitant. In patients on chronic warfarin therapy, the prothrombin time (INR) should be closely monitored in the 2-week period, particularly at 7 to 10 days, following initiation of fosaprepitant with each chemotherapy cycle.

Tolbutamide: Oral aprepitant, 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 orally prior to the administration of the 3-day regimen of oral aprepitant and on Days 4, 8, and 15.

7.2 Effect of Other Agents on the Pharmacokinetics of Aprepitant

Aprepitant is a substrate for CYP3A4; therefore, coadministration of fosaprepitant or aprepitant with drugs that inhibit CYP3A4 activity may result in increased plasma concentrations of aprepitant. Consequently, concomitant administration of fosaprepitant or aprepitant with strong CYP3A4 inhibitors

(e.g., ketoconazole, itraconazole, nefazodone, troleandomycin, clarithromycin, ritonavir, nelfinavir) should be approached with caution. Because moderate CYP3A4 inhibitors (e.g., diltiazem) result in a 2-fold increase in plasma concentrations of aprepitant, concomitant administration should also be approached with caution.

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

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

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

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

7.3 Additional Interactions

Diltiazem: In a study in 10 patients with mild to moderate hypertension, intravenous infusion of 100 mg of fosaprepitant with diltiazem 120 mg 3 times daily, resulted in a 1.5-fold increase of aprepitant AUC and a 1.4-fold increase in diltiazem AUC. It also resulted in a small but clinically meaningful further maximum decrease in diastolic blood pressure [mean (SD) of 24.3 (± 10.2) mm Hg with fosaprepitant versus 15.6 (± 4.1) mm Hg without fosaprepitant] and resulted in a small further maximum decrease in systolic blood pressure [mean (SD) of 29.5 (± 7.9) mm Hg with fosaprepitant versus 23.8 (± 4.8) mm Hg without fosaprepitant], which may be clinically meaningful, but did not result in a clinically meaningful further change in heart rate or PR interval, beyond those changes induced by diltiazem alone.

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

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic effects

Pregnancy Category B: In the reproduction studies conducted with fosaprepitant and aprepitant, the highest systemic exposures to aprepitant were obtained following oral administration of aprepitant. Reproduction studies performed in rats at oral doses of aprepitant up to 1000 mg/kg twice daily (plasma $AUC_{0\text{-}24hr}$ of 31.3 mcg•hr/mL, about 1.6 times the human exposure at the recommended dose) and in rabbits at oral doses up to 25 mg/kg/day (plasma $AUC_{0\text{-}24hr}$ of 26.9 mcg•hr/mL, about 1.4 times the human exposure at the recommended dose) revealed no evidence of impaired fertility or harm to the fetus due to aprepitant. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

8.3 Nursing Mothers

Aprepitant is excreted in the milk of rats. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for possible serious

adverse reactions in nursing infants from aprepitant and because of the potential for tumorigenicity shown for aprepitant in rodent carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

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

8.5 Geriatric Use

In 2 well-controlled chemotherapy-induced nausea and vomiting clinical studies, of the total number of patients (N=544) treated with oral aprepitant, 31% were 65 and over, while 5% were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Greater sensitivity of some older individuals cannot be ruled out. Dosage adjustment in the elderly is not necessary *[see Clinical Pharmacology (12.3)]*.

8.6 Patients with Severe Hepatic Impairment

There are no clinical or pharmacokinetic data in patients with severe hepatic impairment (Child-Pugh score >9). Therefore, caution should be exercised when fosaprepitant or aprepitant is administered in these patients *[see Clinical Pharmacology (12.3)].*

10 OVERDOSAGE

There is no specific information on the treatment of overdosage with fosaprepitant or aprepitant.

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

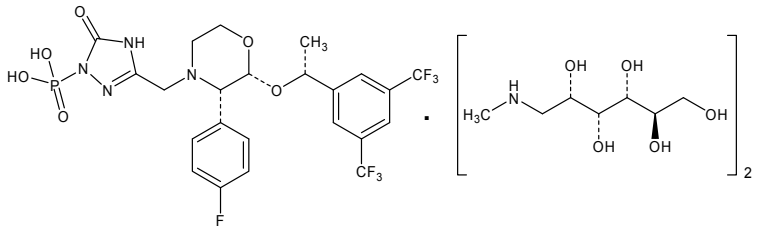
Aprepitant cannot be removed by hemodialysis.

Thirteen patients in the randomized controlled trial of EMEND for Injection received both fosaprepitant 150 mg and at least one dose of oral aprepitant, 125 mg or 80 mg. Three patients reported adverse reactions that were similar to those experienced by the total study population.

11 DESCRIPTION

EMEND (fosaprepitant dimeglumine) for Injection is a sterile, lyophilized prodrug of aprepitant, a substance P/neurokinin-1 (NK_1) receptor antagonist, and is chemically described as 1-Deoxy-1-(methylamino)-D-glucitol[3-[[(2*R*,3*S*)-2-[(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-2,5-dihydro-5-oxo-1*H*-1,2,4-triazol-1-yl]phosphonate (2:1) (salt).

Its empirical formula is $C_{23}H_{22}F_7N_4O_6P \cdot 2(C_7H_{17}NO_5)$ and its structural formula is:



Fosaprepitant dimeglumine is a white to off-white amorphous powder with a molecular weight of 1004.83. It is freely soluble in water.

EMEND for Injection is a lyophilized prodrug of aprepitant containing polysorbate 80 (PS80), to be administered intravenously as an infusion.

Each vial of EMEND for Injection 115 mg for intravenous administration contains 188 mg of fosaprepitant dimeglumine equivalent to 115 mg of fosaprepitant free acid and the following inactive ingredients: edetate disodium (14.4 mg), polysorbate 80 (57.5 mg), lactose anhydrous (287.5 mg), sodium hydroxide and/or hydrochloric acid (for pH adjustment). Each vial of EMEND for Injection 150 mg

for intravenous administration contains 245.3 mg of fosaprepitant dimeglumine equivalent to 150 mg of fosaprepitant free acid and the following inactive ingredients: edetate disodium (18.8 mg), polysorbate 80 (75 mg), lactose anhydrous (375 mg), sodium hydroxide and/or hydrochloric acid (for pH adjustment). Fosaprepitant dimeglumine hereafter will be referred to as fosaprepitant.

12 CLINICAL PHARMACOLOGY

Fosaprepitant, a prodrug of aprepitant, when administered intravenously is rapidly converted to aprepitant, a substance P/neurokinin 1 (NK_1) receptor antagonist. Plasma concentrations of fosaprepitant are below the limits of quantification (10 ng/mL) within 30 minutes of the completion of infusion *[see Clinical Pharmacology (12.3)]*. Upon conversion of 188 mg of fosaprepitant dimeglumine (equivalent to 115-mg fosaprepitant free acid) to aprepitant, 18.3 mg of phosphoric acid and 73 mg of meglumine are liberated. Upon conversion of 245.3 mg of fosaprepitant dimeglumine (equivalent to 150-mg fosaprepitant free acid) to aprepitant, 23.9 mg of phosphoric acid and 95.3 mg of meglumine are liberated.

12.1 Mechanism of Action

Fosaprepitant is a prodrug of aprepitant and accordingly, its antiemetic effects are attributable to aprepitant.

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). 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 control studies, healthy young men received oral aprepitant doses of 10 mg (N=2), 30 mg (N=3), 100 mg (N=3) or 300 mg (N=5) once daily 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 aprepitant regimen for CINV produces mean trough plasma aprepitant concentrations >500 ng/mL, which would be expected to, based on the fitted curve with the Hill equation, result in >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 aprepitant has not been established.

Cardiac Electrophysiology

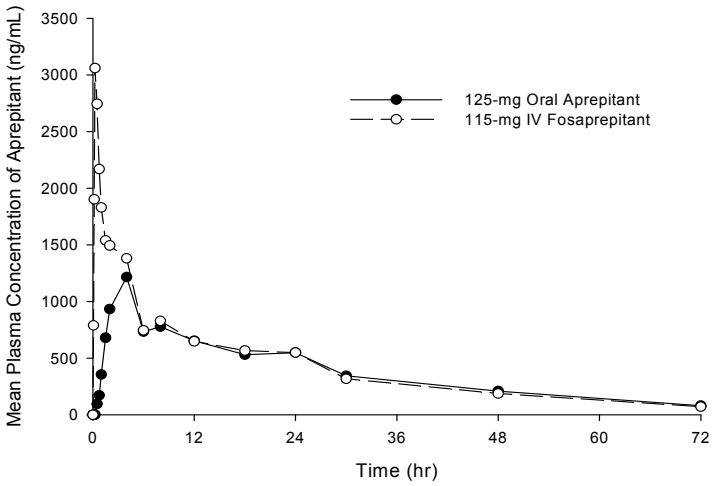
In a randomized, double-blind, positive-controlled, thorough QTc study, a single 200-mg dose of fosaprepitant had no effect on the QTc interval.

12.3 Pharmacokinetics

Aprepitant after Fosaprepitant Administration

Following a single intravenous 115-mg dose of fosaprepitant administered as a 15-minute infusion to healthy volunteers the mean $AUC_{0-\infty}$ of aprepitant was 31.7 (± 14.3) mcg•hr/mL and the mean maximal aprepitant concentration (C_{max}) was 3.27 (± 1.16) mcg/mL. The mean aprepitant plasma concentration at 24 hours postdose was similar between the 125-mg oral aprepitant dose and the 115-mg intravenous fosaprepitant dose. (See Figure 1.)

Figure 1: Mean Plasma Concentration of Aprepitant Following 125-mg Oral Aprepitant and 115-mg Intravenous Fosaprepitant



Following a single, intravenous 150-mg dose of fosaprepitant administered as a 20-minute infusion to healthy volunteers, the mean $AUC_{0-\infty}$ of aprepitant was 37.38 (± 14.75) mcg•hr/mL and the mean maximal aprepitant concentration (C_{max}) was 4.15 (± 1.15) mcg/mL.

Distribution

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

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

Metabolism

Fosaprepitant was rapidly converted to aprepitant in *in vitro* incubations with liver preparations from nonclinical species (rat and dog) and humans. Furthermore, fosaprepitant underwent rapid and nearly complete conversion to aprepitant in S9 preparations from multiple other human tissues including kidney, lung and ileum. Thus, it appears that the conversion of fosaprepitant to aprepitant can occur in multiple extrahepatic tissues in addition to the liver. In humans, fosaprepitant administered intravenously was rapidly converted to aprepitant within 30 minutes following the end of infusion.

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

Excretion

Following administration of a single intravenous 100-mg dose of [^{14}C]-fosaprepitant to healthy subjects, 57% of the radioactivity was recovered in urine and 45% in feces.

Aprepitant is eliminated primarily by metabolism; aprepitant is not renally excreted. The apparent terminal half-life ranged from approximately 9 to 13 hours.

Specific Populations

Gender

Following oral administration of a single dose of aprepitant, the AUC_{0-24hr} and C_{max} are 14% and 22% higher in females as compared with males. The half-life of aprepitant is 25% lower in females as

compared with males and T_{max} occurs at approximately the same time. These differences are not considered clinically meaningful. No dosage adjustment is necessary based on gender.

Geriatric

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

Race

Following oral administration of a single dose of aprepitant, the $AUC_{0\text{-}24hr}$ and C_{max} are approximately 42% and 29% higher in Hispanics as compared with Caucasians. The $AUC_{0\text{-}24hr}$ and C_{max} are 62% and 41% 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. No dosage adjustment is necessary based on race.

Body Mass Index (BMI)

For every 5 kg/m^2 increase in BMI, $AUC_{0\text{-}24hr}$ and C_{max} of aprepitant decrease by 11%. BMI of subjects in the analysis ranged from 18 kg/m^2 to 36 kg/m^2. This change is not considered clinically meaningful. No dosage adjustment is necessary based on BMI.

Hepatic Insufficiency

Fosaprepitant is metabolized in various extrahepatic tissues; therefore hepatic impairment is not expected to alter the conversion of fosaprepitant to aprepitant.

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

There are no clinical or pharmacokinetic data in patients with severe hepatic impairment (Child-Pugh score >9) *[see Use in Specific Populations (8.6)]*.

Renal Insufficiency

A single 240-mg dose of oral aprepitant was administered to patients with severe renal impairment (creatinine clearance <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 $AUC_{0\text{-}\infty}$ of total aprepitant (unbound and protein bound) decreased by 21% and C_{max} decreased by 32%, relative to healthy subjects (creatinine clearance >80 mL/min estimated by Cockcroft-Gault method). In patients with ESRD undergoing hemodialysis, the $AUC_{0\text{-}\infty}$ 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.

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies were conducted in Sprague-Dawley rats and in CD-1 mice for 2 years. In the rat carcinogenicity studies, animals were treated with oral doses ranging from 0.05 to 1000 mg/kg twice daily. The highest dose produced a systemic exposure to aprepitant (plasma $AUC_{0\text{-}24hr}$) of 0.7 to

1.6 times the human exposure ($AUC_{0\text{-}24hr}$ = 19.6 mcg•hr/mL) at the recommended dose of 125 mg/day. Treatment with aprepitant at doses of 5 to 1000 mg/kg twice daily caused an increase in the incidences of thyroid follicular cell adenomas and carcinomas in male rats. In female rats, it produced hepatocellular adenomas at 5 to 1000 mg/kg twice daily and hepatocellular carcinomas and thyroid follicular cell adenomas at 125 to 1000 mg/kg twice daily. In the mouse carcinogenicity studies, the animals were treated with oral doses ranging from 2.5 to 2000 mg/kg/day. The highest dose produced a systemic exposure of about 2.8 to 3.6 times the human exposure at the recommended dose. Treatment with aprepitant produced skin fibrosarcomas at 125 and 500 mg/kg/day doses in male mice. Carcinogenicity studies were not conducted with fosaprepitant.

Aprepitant and fosaprepitant were 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.

Fosaprepitant, when administered intravenously, is rapidly converted to aprepitant. In the fertility studies conducted with fosaprepitant and aprepitant, the highest systemic exposures to aprepitant were obtained following oral administration of aprepitant. Oral aprepitant did not affect the fertility or general reproductive performance of male or female rats at doses up to the maximum feasible dose of 1000 mg/kg twice daily (providing exposure in male rats lower than the exposure at the recommended human dose and exposure in female rats at about 1.6 times the human exposure).

14 CLINICAL STUDIES

Fosaprepitant, a prodrug of aprepitant, when administered intravenously is rapidly converted to aprepitant.

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

14.1 Highly Emetogenic Chemotherapy (HEC)

EMEND for Injection 115 mg (3-Day Dosing Regimen of EMEND)

Fosaprepitant 115 mg intravenous infused over 15 minutes can be substituted for 125 mg oral aprepitant on Day 1 of a 3-day regimen. Efficacy studies with the 3-day regimen were conducted with oral aprepitant.

In 2 multicenter, randomized, parallel, double-blind, controlled clinical studies, the aprepitant regimen (see Table 11) was compared with standard therapy in patients receiving a chemotherapy regimen that included cisplatin >50 mg/m^2 (mean cisplatin dose = 80.2 mg/m^2). Of the 550 patients who were randomized to receive the aprepitant regimen, 42% were women, 58% men, 59% White, 3% Asian, 5% Black, 12% Hispanic American, and 21% Multi-Racial. The aprepitant-treated patients in these clinical studies ranged from 14 to 84 years of age, with a mean age of 56 years. 170 patients were 65 years or older, with 29 patients being 75 years or older.

Patients (N = 1105) were randomized to either the aprepitant regimen (N = 550) or standard therapy (N = 555). The treatment regimens are defined in Table 11.

Table 11
Treatment Regimens
Highly Emetogenic Chemotherapy Trials*

	Day 1	Day 2	Day 3	Day 4
CINV Aprepitant Regimen				
Aprepitant	125 mg orally	80 mg orally	80 mg orally	none
Dexamethasone	12 mg orally	8 mg orally	8 mg orally	8 mg orally
5-HT_3 antagonist†	See package insert	none	none	none
CINV Standard Therapy				
Dexamethasone	20 mg orally	8 mg orally twice daily	8 mg orally twice daily	8 mg orally twice daily
5-HT_3 antagonist†	See package insert	none	none	none

*Aprepitant placebo and dexamethasone placebo were used to maintain blinding.
†Ondansetron 32 mg I.V. was used in the clinical trials of aprepitant. Although this dose was used in clinical trials, this is no longer the currently recommended dose. Refer to the ondansetron package insert for the current dosing.

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

The antiemetic activity of oral aprepitant 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 <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 <5 mm on a 0 to 100 mm scale)
- no significant nausea (maximum VAS <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 12 and in Table 13.

Table 12
Percent of Patients Receiving Highly Emetogenic Chemotherapy Responding by Treatment Group and Phase for Study 1 — Cycle 1

ENDPOINTS	Aprepitant Regimen (N = 260)[†] %	Standard Therapy (N = 261)[†] %	p-Value
PRIMARY ENDPOINT			
Complete Response			
Overall[‡]	73	52	<0.001
OTHER PRESPECIFIED ENDPOINTS			
Complete Response			
Acute phase[§]	89	78	<0.001
Delayed phase[‖]	75	56	<0.001
Complete Protection			
Overall	63	49	0.001
Acute phase	85	75	NS*
Delayed phase	66	52	<0.001
No Emesis			
Overall	78	55	<0.001
Acute phase	90	79	0.001
Delayed phase	81	59	<0.001
No Nausea			
Overall	48	44	NS**
Delayed phase	51	48	NS**
No Significant Nausea			
Overall	73	66	NS**
Delayed phase	75	69	NS**

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

Table 13
Percent of Patients Receiving Highly Emetogenic Chemotherapy Responding by Treatment Group and Phase for Study 2 — Cycle 1

ENDPOINTS	Aprepitant Regimen (N = 261)[†] %	Standard Therapy (N = 263)[†] %	p-Value
PRIMARY ENDPOINT			
Complete Response			
Overall[‡]	63	43	<0.001
OTHER PRESPECIFIED ENDPOINTS			
Complete Response			
Acute phase[§]	83	68	<0.001
Delayed phase[‖]	68	47	<0.001
Complete Protection			
Overall	56	41	<0.001
Acute phase	80	65	<0.001
Delayed phase	61	44	<0.001
No Emesis			
Overall	66	44	<0.001
Acute phase	84	69	<0.001
Delayed phase	72	48	<0.001
No Nausea			

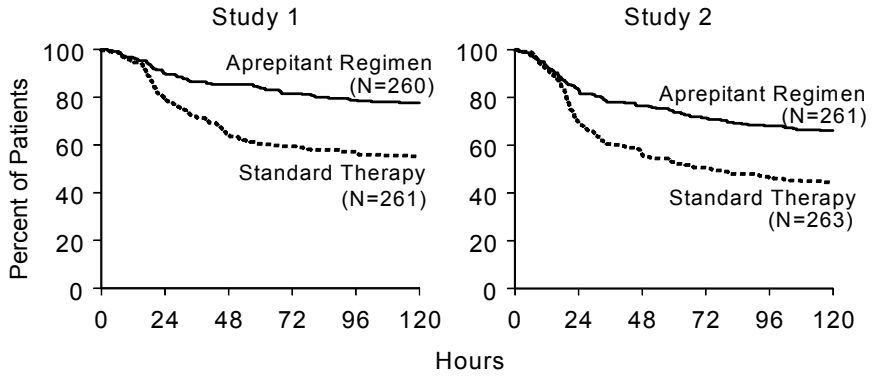
Overall	49	39	NS*
Delayed phase	53	40	NS*
No Significant Nausea			
Overall	71	64	NS**
Delayed phase	73	65	NS**

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

In both studies, a statistically significantly higher proportion of patients (both p<0.001) receiving the aprepitant 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 aprepitant regimen was also observed when the acute phase and the delayed phase were analyzed separately.

In both studies, the estimated time to first emesis after initiation of cisplatin treatment was longer with the aprepitant regimen, and the incidence of first emesis was reduced in the aprepitant regimen group compared with standard therapy group as depicted in the Kaplan-Meier curves in Figure 2.

Figure 2: Percent of Patients Receiving Highly Emetogenic Chemotherapy Who Remain Emesis Free Over Time — Cycle 1

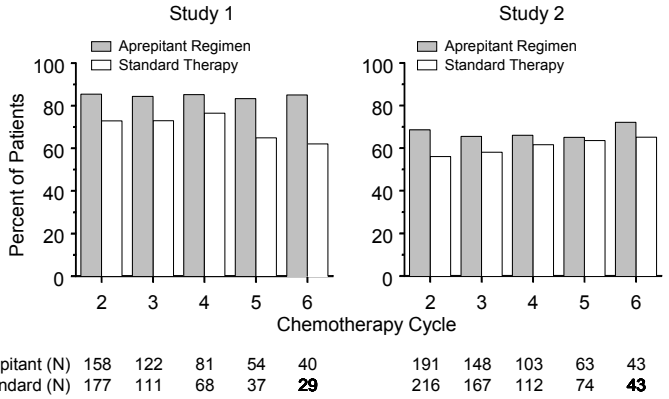


p-Value <0.001 based on a log rank test for Study 1 and Study 2; nominal p-values not adjusted for multiplicity.

Additional Patient-Reported Outcomes: The impact of nausea and vomiting on patients' daily lives was assessed in Cycle 1 of both phase 3 studies using the Functional Living Index–Emesis (FLIE), a validated nausea- and vomiting-specific patient-reported outcome measure. Minimal or no impact of nausea and vomiting on patients' daily lives is defined as a FLIE total score >108. In each of the 2 studies, a higher proportion of patients receiving the aprepitant regimen reported minimal or no impact of nausea and vomiting on daily life (Study 1: 74% versus 64%; Study 2: 75% versus 64%).

Multiple-Cycle Extension: In the same 2 clinical studies, patients continued into the Multiple-Cycle extension for up to 5 additional cycles of chemotherapy. The proportion of patients with no emesis and no significant nausea by treatment group at each cycle is depicted in Figure 3.

Figure 3: Proportion of Patients Receiving Highly Emetogenic Chemotherapy with No Emesis and No Significant Nausea by Treatment Group and Cycle



EMEND for Injection 150 mg (Single Dose Regimen of EMEND)

EMEND for Injection 150 mg infused over 20-30 minutes is administered on Day 1 only and can be substituted for the 3-day dosing regimen of EMEND for the prevention of nausea and vomiting induced by HEC.

In a randomized, parallel, double-blind, active-controlled study, EMEND for Injection 150 mg (N=1147) was compared with a 3-day oral aprepitant regimen (N=1175) (see Table 14 below) in patients receiving a highly emetogenic chemotherapy regimen that included cisplatin (≥70 mg/m^2). Patient demographics were similar between the two treatment groups. Of the total 2322 patients receiving EMEND for Injection or oral aprepitant, 63% were men, 56% White, 26% Asian, 3% American Indian/Alaska Native, 2% Black, 13% Multi-Racial, and 33% Hispanic/Latino ethnicity. Patient ages ranged from 19 to 86 years of age, with a mean age of 56 years. Other concomitant chemotherapy agents were administered similar to those in prior HEC studies described above.

Table 14
Treatment Regimens
Highly Emetogenic Chemotherapy Trial*

	Day 1	Day 2	Day 3	Day 4
CINV Fosaprepitant Regimen				
Fosaprepitant	150 mg intravenously	none	none	none
Dexamethasone	12 mg orally	8 mg orally	8 mg orally twice daily	8 mg orally twice daily
5-HT$_3$ antagonist†	See package insert	none	none	none
CINV Aprepitant Regimen				
Aprepitant	125 mg orally	80 mg orally	80 mg orally	none
Dexamethasone	12 mg orally	8 mg orally	8 mg orally	8 mg orally
5-HT$_3$ antagonist†	See package insert	none	none	none

*Fosaprepitant placebo, aprepitant placebo and dexamethasone placebo (in the evenings on Days 3 and 4) were used to maintain blinding.

†Ondansetron 32 mg I.V. was used in the clinical trial of EMEND for Injection. Although this dose was used in the clinical trial, this is no longer the currently recommended dose. Refer to the ondansetron package insert for the current dosing.

The efficacy of fosaprepitant 150 mg was evaluated based on the primary and secondary endpoints listed in Table 15 below and was shown to be non-inferior to that of the 3-day oral aprepitant regimen with regard to complete response in each of the evaluated phases. The pre-specified non-inferiority margin for complete response in the overall phase was 7%. The pre-specified non-inferiority margin for complete

response in the delayed phase was 7.3%. The pre-specified non-inferiority margin for no vomiting in the overall phase was 8.2%.

Table 15
Percent of Patients Receiving Highly Emetogenic Chemotherapy Responding by Treatment Group and Phase — Cycle 1

ENDPOINTS	Fosaprepitant Regimen (N = 1106)** %	Aprepitant Regimen (N = 1134)** %	Difference† (95% CI)
PRIMARY ENDPOINT			
Complete Response‡			
Overall§	71.9	72.3	-0.4 (-4.1, 3.3)
SECONDARY ENDPOINTS			
Complete Response‡			
Delayed phase§§	74.3	74.2	0.1 (-3.5, 3.7)
No Vomiting			
Overall§	72.9	74.6	-1.7 (-5.3, 2.0)

**N: Number of patients included in the primary analysis of complete response.
†Difference and Confidence interval (CI) were calculated using the method proposed by Miettinen and Nurminen and adjusted for Gender.
‡Complete Response = no vomiting and no use of rescue therapy.
§Overall = 0 to 120 hours post-initiation of cisplatin chemotherapy.
§§Delayed phase = 25 to 120 hours post-initiation of cisplatin chemotherapy.

14.2 Moderately Emetogenic Chemotherapy (MEC)

In a multicenter, randomized, double-blind, parallel-group, clinical study in breast cancer patients, the aprepitant regimen (see Table 16) was compared with a standard of care therapy in patients receiving a moderately emetogenic chemotherapy regimen that included cyclophosphamide 750-1500 mg/m^2; or cyclophosphamide 500-1500 mg/m^2 and doxorubicin (≤60 mg/m^2) or epirubicin (≤100 mg/m^2).

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

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

Patients (N = 866) were randomized to either the aprepitant regimen (N = 438) or standard therapy (N = 428). The treatment regimens are defined in Table 16.

Table 16
Treatment Regimens
Moderately Emetogenic Chemotherapy Trial*

	Day 1	Day 2	Day 3
CINV Aprepitant Regimen			
Aprepitant	125 mg orally**	80 mg orally	80 mg orally
Dexamethasone	12 mg orally†	none	none
Ondansetron	8 mg orally x 2 doses‡	none	none
CINV Standard Therapy			
Dexamethasone	20 mg orally	none	none
Ondansetron	8 mg orally x 2 doses	8 mg orally twice daily	8 mg orally twice daily

*Aprepitant placebo and dexamethasone placebo were used to maintain blinding.
**1 hour prior to chemotherapy.
†Dexamethasone was administered 30 minutes prior to chemotherapy treatment on Day 1.
‡Ondansetron was administered 30 to 60 minutes prior to chemotherapy treatment on Day 1 and 8 hours after first ondansetron dose.

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

A summary of the key results from this study is shown in Table 17.

Table 17
Percent of Patients Receiving Moderately Emetogenic Chemotherapy Responding by Treatment Group and Phase — Cycle 1

ENDPOINTS	Aprepitant 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.

In this study, a statistically significantly (p=0.015) higher proportion of patients receiving the aprepitant regimen in Cycle 1 had a complete response (primary endpoint) during the overall phase compared with patients receiving standard therapy. 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 aprepitant regimen in Cycle 1 had a complete response during the acute (0-24 hours) and delayed (25-120 hours) phases compared with patients receiving standard therapy; however, the treatment group differences failed to reach statistical significance, after multiplicity adjustments.

Additional Patient-Reported Outcomes: In a phase 3 study in patients receiving moderately emetogenic chemotherapy, the impact of nausea and vomiting on patients’ daily lives was assessed in Cycle 1 using the FLIE. A higher proportion of patients receiving the aprepitant regimen reported minimal or no impact on daily life (64% versus 56%). This difference between treatment groups was primarily driven by the “No Vomiting Domain” of this composite endpoint.

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

Postmarketing Trial: In a postmarketing, multicenter, randomized, double-blind, parallel-group, clinical study in 848 cancer patients, the aprepitant regimen (N=430) was compared with a standard of care therapy (N=418) in patients receiving a moderately emetogenic chemotherapy regimen that included any IV dose of oxaliplatin, carboplatin, epirubicin, idarubicin, ifosfamide, irinotecan, daunorubicin, doxorubicin; cyclophosphamide IV (<1500 mg/m^2); or cytarabine IV (>1 g/m^2).

Of the 430 patients who were randomized to receive the aprepitant 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 aprepitant-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. Patients receiving the aprepitant 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.

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 this study is shown in Table 18.

Table 18
Percent of Patients Receiving Moderately Emetogenic Chemotherapy Responding by Treatment Group for Study 2 — Cycle 1

ENDPOINTS	Aprepitant 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.

In this study, a statistically significantly higher proportion of patients receiving the aprepitant 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 aprepitant 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 aprepitant 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 aprepitant 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 aprepitant were observed to have no vomiting and complete response compared to patients receiving standard therapy. For gender, the difference in complete response rates between the aprepitant 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 gender was observed for the no vomiting endpoint.

16 HOW SUPPLIED/STORAGE AND HANDLING

No. 3884 — One 115-mg single dose glass vial: White to off-white lyophilized solid. Supplied as follows:

NDC 0006-3884-32 1 vial per carton.

No. 3941 — One 150-mg single dose glass vial: White to off-white lyophilized solid. Supplied as follows:

NDC 0006-3941-32 1 vial per carton.

Storage

Vials: Store at 2-8°C (36-46°F).

Sterile lyophilized powder for intravenous use only after reconstitution and dilution.

17 PATIENT COUNSELING INFORMATION

"See FDA-Approved Patient Labeling (Patient Information)"

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

Patients should follow the physician's instructions for the EMEND for Injection regimen.

Allergic reactions, which may be sudden and/or serious, and may include hives, rash, itching, redness of the face/skin and may cause difficulty in breathing or swallowing, have been reported. Physicians should instruct their patients to stop using EMEND and call their doctor right away if they experience an allergic reaction. In addition, severe skin reactions may occur rarely.

Patients who develop an infusion site reaction such as erythema, edema, pain, or thrombophlebitis should be instructed on how to care for the local reaction and when to seek further evaluation.

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

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

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

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