CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

022023Orig1s018

Trade Name: **EMEND**

Generic Name: Fosaprepitant

Sponsor: Merck Sharp & Dohme Corp.

Approval Date: 03/26/2018

Indications: EMEND for injection is a substance P/neurokinin-1 (NK1) receptor antagonist, indicated in adults, in combination with other antiemetic agents, for the prevention of (1):

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

- delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC).

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APPLICATION NUMBER:

022023Orig1s018

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	
Labeling	**X**
Summary Review	
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	
Medical Review(s)	**X**
Chemistry Review(s)	
Environmental Assessment	
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Other Review(s)	
Administrative/Correspondence Document(s)	**X**

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APPLICATION NUMBER:

022023Orig1s018

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22023-S18

SUPPLEMENT APPROVAL

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
Attention: Nicholas W. Andrew
Director, Regulatory Affairs
126 E. Lincoln Avenue
P.O. Box 2000, RY34-B293
Rahway, NJ 07065-0900

Dear Mr. Andrew:

Please refer to your Supplemental New Drug Application (sNDA) dated February 22, 2018, received and submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Emend (fosaprepitant) for injection.

We also refer to our letter dated January 23, 2018, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for EMEND (fosaprepitant). This information pertains to the risk of infusion site reaction.

APPROVAL & LABELING

We have completed our review of this supplemental application. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

We note that your March 22, 2018, submission includes final printed labeling (FPL) for your package insert, patient package insert, Medication Guide. We have not reviewed this FPL. You are responsible for assuring that the wording in this printed labeling is identical to that of the approved content of labeling in the structured product labeling (SPL) format.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient package insert, Medication Guide), with the addition of any labeling changes in pending “Changes Being Effected” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Mary Chung, Senior Regulatory Project Manager, at (301) 796-0260.

Sincerely,

{See appended electronic signature page}

Joyce Korvick, M.D, M.P.H.
Deputy Director, Safety
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOYCE A KORVICK
03/26/2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022023Orig1s018

LABELING

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

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

----------RECENT MAJOR CHANGES----------

Warnings and Precautions (5.2)	08/2017
Warnings and Precautions (5.3)	03/2018

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

EMEND® for injection is a substance P/neurokinin-1 (NK_1) receptor antagonist, indicated in adults, in combination with other antiemetic agents, for the prevention of (1):

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

Limitations of Use (1)

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

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

Dosage (2.1)

- Recommended dosage in adults is 150 mg on Day 1 as an intravenous infusion over 20 to 30 minutes approximately 30 minutes prior to chemotherapy.
- See Full Prescribing Information for recommended dosages of concomitant dexamethasone and a 5-HT_3 antagonist for HEC and MEC.

Preparation (2.2)

- Reconstitute with 5 mL of 0.9% sodium chloride.
- Add to infusion bag containing 145 mL 0.9% sodium chloride for a final concentration of 1 mg/mL.

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

EMEND for injection: 150 mg fosaprepitant, lyophilized powder in single-dose vial for reconstitution. (3)

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

- Known hypersensitivity to any component of this drug. (4, 5.2)
- Concurrent use with pimozide. (4)

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

- CYP3A4 Interactions: Fosaprepitant is a weak inhibitor of CYP3A4, and aprepitant, the active moiety, is a substrate, inhibitor, and inducer of CYP3A4; see Full Prescribing Information for recommendations regarding contraindications, risk of adverse reactions, and dosage adjustment of EMEND and concomitant drugs. (4, 5.1, 7.1, 7.2)
- Hypersensitivity Reactions (including anaphylaxis and anaphylactic shock): May occur during or soon after infusion. If symptoms occur, discontinue the drug. Do not reinitiate EMEND if symptoms occur with first-time use. (4, 5.2)
- Infusion Site Reactions (including thrombophlebitis, necrosis, and vasculitis): Majority of reactions reported in patients receiving vesicant chemotherapy. Avoid infusion into small veins. Discontinue infusion and administer treatment if a severe reaction develops. (5.3)
- Warfarin (a CYP2C9 substrate): Risk of decreased INR of prothrombin time; monitor INR in 2–week period, particularly at 7 to 10 days, following initiation of EMEND. (5.4, 7.1)
- Hormonal Contraceptives: Efficacy of contraceptives may be reduced during and for 28 days following administration of EMEND. Use effective alternative or back-up methods of contraception. (5.5, 7.1, 8.3)

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

Most common adverse reactions (≥2%) are: fatigue, diarrhea, neutropenia, asthenia, anemia, peripheral neuropathy, leukopenia, dyspepsia, urinary tract infection, pain in extremity. (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----------

See Full Prescribing Information for a list of clinically significant drug interactions. (4, 5.1, 5.4, 5.5, 7.1, 7.2)

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

Revised: 03/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Prevention of Nausea and Vomiting Associated with HEC and MEC
2.2 Preparation of EMEND for Injection
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Clinically Significant CYP3A4 Drug Interactions
5.2 Hypersensitivity Reactions
5.3 Infusion Site Reactions
5.4 Decrease in INR with Concomitant Warfarin
5.5 Risk of Reduced Efficacy of Hormonal Contraceptives
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Postmarketing Experience
7 DRUG INTERACTIONS
7.1 Effect of Fosaprepitant/Aprepitant on the Pharmacokinetics of Other Drugs
7.2 Effect of Other Drugs on the Pharmacokinetics of Fosaprepitant/Aprepitant
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.3 Females and Males of Reproductive Potential
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Patients with Hepatic Impairment
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
14.1 Prevention of Nausea and Vomiting Associated with HEC
14.2 Prevention of Nausea and Vomiting Associated with MEC
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

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

Reference ID: 4239669

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

EMEND® for injection, in combination with other antiemetic agents, is indicated in adults 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.
- delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC).

Limitations of Use

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

2 DOSAGE AND ADMINISTRATION

2.1 Prevention of Nausea and Vomiting Associated with HEC and MEC

The recommended dosage of EMEND for injection, dexamethasone, and a 5-HT_3 antagonist in adults for the prevention of nausea and vomiting associated with administration of HEC or MEC is shown in Table 1 or Table 2, respectively. Administer EMEND for injection as an intravenous infusion on Day 1 over 20 to 30 minutes approximately 30 minutes prior to chemotherapy.

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

	Day 1	Day 2	Day 3	Day 4
EMEND for injection	150 mg intravenously over 20 to 30 minutes approximately 30 minutes prior to chemotherapy	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 selected 5-HT_3 antagonist prescribing information for the recommended dosage	none	none	none

*Administer dexamethasone 30 minutes prior to chemotherapy treatment on Day 1 and in the morning on Days 2 through 4. Also administer dexamethasone in the evenings on Days 3 and 4. A 50% dosage reduction of dexamethasone on Days 1 and 2 is recommended to account for a drug interaction with EMEND *[see Clinical Pharmacology (12.3)]*.

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

	Day 1
EMEND for injection	150 mg intravenously over 20 to 30 minutes approximately 30 minutes prior to chemotherapy
Dexamethasone*	12 mg orally
5-HT_3 antagonist	See selected 5-HT_3 antagonist prescribing information for the recommended dosage

*Administer dexamethasone 30 minutes prior to chemotherapy treatment on Day 1. A 50% dosage reduction of dexamethasone is recommended to account for a drug interaction with EMEND *[see Clinical Pharmacology (12.3)]*.

Reference ID: 4239669

2.2 Preparation of EMEND for Injection

Table 3
Preparation Instructions for EMEND for Injection

Step 1	Aseptically inject 5 mL 0.9% Sodium Chloride Injection, USP into the vial. Assure that 0.9% Sodium Chloride Injection, USP is added to the vial along the vial wall in order to prevent foaming. Swirl the vial gently. Avoid shaking and jetting 0.9% Sodium Chloride Injection, USP into the vial.
Step 2	Aseptically prepare an infusion bag filled with **145 mL** of 0.9% Sodium Chloride Injection, USP.
Step 3	Aseptically withdraw the entire volume from the vial and transfer it into the infusion bag containing **145 mL** of 0.9% Sodium Chloride Injection, USP to yield a total volume of **150 mL** and a final concentration of 1 mg/mL**.**
Step 4	Gently invert the bag 2 to 3 times.
Step 5	Before administration, inspect the bag for particulate matter and discoloration. Discard the bag if particulate and/or discoloration are observed.

Caution: Do not mix or reconstitute EMEND for injection 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.

Storage

The reconstituted final drug solution is stable for 24 hours at ambient room temperature [at or below 25°C (77°F)].

3 DOSAGE FORMS AND STRENGTHS

EMEND for injection: 150 mg fosaprepitant, white to off-white lyophilized powder in single-dose glass vial for reconstitution

4 CONTRAINDICATIONS

EMEND is contraindicated in patients:

- who are hypersensitive to any component of the product. Hypersensitivity reactions including anaphylactic reactions, flushing, erythema, and dyspnea have been reported *[see Warnings and Precautions (5.2), Adverse Reactions (6.2)]*.

- taking pimozide. Inhibition of CYP3A4 by aprepitant, the active moiety, could result in elevated plasma concentrations of this drug, which is a CYP3A4 substrate, potentially causing serious or life-threatening reactions, such as QT prolongation, a known adverse reaction of pimozide *[see Warnings and Precautions (5.1)].*

5 WARNINGS AND PRECAUTIONS

5.1 Clinically Significant CYP3A4 Drug Interactions

Fosaprepitant, a prodrug of aprepitant, is a weak inhibitor of CYP3A4, and aprepitant is a substrate, inhibitor, and inducer of CYP3A4.

Reference ID: 4239669

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

See Table 5 and Table 6 for a listing of potentially significant drug interactions *[see Drug Interactions (7.1, 7.2)].*

5.2 Hypersensitivity Reactions

Serious hypersensitivity reactions, including anaphylaxis and anaphylactic shock, during or soon after infusion of fosaprepitant have occurred. Symptoms including flushing, erythema, dyspnea, hypotension and syncope have been reported *[see Adverse Reactions (6.2)]*.

Monitor patients during and after infusion. If hypersensitivity reactions occur, discontinue the infusion and administer appropriate medical therapy. Do not reinitiate EMEND in patients who experience these symptoms with first-time use *[see Contraindications (4)]*.

5.3 Infusion Site Reactions

Infusion site reactions (ISRs) have been reported with the use of EMEND for injection *[see Adverse Reactions (6.1)]*. The majority of severe ISRs, including thrombophlebitis and vasculitis, were reported with concomitant vesicant (anthracycline-based) chemotherapy administration, particularly when associated with extravasation. Necrosis was also reported in some patients with concomitant vesicant chemotherapy. Most ISRs occurred with the first, second or third exposure to single doses of EMEND for injection and in some cases, reactions persisted for two weeks or longer. Treatment of severe ISRs consisted of medical, and in some cases surgical, intervention.

Avoid infusion of EMEND for injection into small veins or through a butterfly catheter. If a severe ISR develops during infusion, discontinue the infusion and administer appropriate medical treatment.

5.4 Decrease in INR with Concomitant Warfarin

Coadministration of EMEND with warfarin, a CYP2C9 substrate, may result in a clinically significant decrease in the International Normalized Ratio (INR) of prothrombin time *[see Clinical Pharmacology (12.3)]*. Monitor the INR in patients on chronic warfarin therapy in the 2-week period, particularly at 7 to 10 days, following initiation of EMEND with each chemotherapy cycle *[see Drug Interactions (7.1)]*.

5.5 Risk of Reduced Efficacy of Hormonal Contraceptives

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

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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

The overall safety of EMEND for injection was evaluated in approximately 1600 individuals.

<u>Adverse Reactions for the Prevention of Nausea and Vomiting Associated with MEC</u>

In an active-controlled clinical trial in patients receiving MEC, safety was evaluated in 504 patients receiving a single dose of EMEND for injection in combination with ondansetron and dexamethasone (EMEND regimen) compared to 497 patients receiving ondansetron and dexamethasone alone (standard therapy). The most common adverse reactions are listed in Table 4.

Table 4
Most Common Adverse Reactions in Patients Receiving MEC*

	EMEND for injection, ondansetron, and dexamethasone† **(N=504)**	**Ondansetron and dexamethasone‡** **(N=497)**
fatigue	15%	13%
diarrhea	13%	11%
neutropenia	8%	7%
asthenia	4%	3%
anemia	3%	2%
peripheral neuropathy	3%	2%
leukopenia	2%	1%
dyspepsia	2%	1%
urinary tract infection	2%	1%
pain in extremity	2%	1%

*Reported in ≥ 2% of patients treated with the EMEND regimen and at a greater incidence than standard therapy.
†EMEND regimen
‡Standard therapy

Infusion-site reactions were reported in 2.2% of patients treated with the EMEND regimen compared to 0.6% of patients treated with standard therapy. The infusion-site reactions included: infusion-site pain (1.2%, 0.4%), injection-site irritation (0.2%, 0.0%), vessel puncture-site pain (0.2%, 0.0%), and infusion-site thrombophlebitis (0.6%, 0.0%), reported in the EMEND regimen compared to standard therapy, respectively.

Adverse Reactions for the Prevention of Nausea and Vomiting Associated with HEC

In an active-controlled clinical study in patients receiving HEC, safety was evaluated for 1143 patients receiving a single dose of EMEND for injection compared to 1169 patients receiving the 3-day regimen of oral EMEND (aprepitant) *[see Clinical Studies (14.1)]*. The safety profile was generally similar to that seen in the MEC study with fosaprepitant and 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 following additional infusion-site reactions occurred in the HEC study and were not reported in the MEC study described above: infusion-site erythema (0.5%, 0.1%), infusion-site pruritus (0.3%, 0.0%), and infusion-site induration (0.2%, 0.1%), reported in the fosaprepitant group compared to the aprepitant group, respectively.

Since fosaprepitant is converted to aprepitant, those adverse reactions associated with aprepitant might also be expected to occur with EMEND for injection. See the full prescribing information for EMEND capsules for complete safety information regarding studies performed with oral aprepitant.

6.2 Postmarketing Experience

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

Skin and subcutaneous tissue disorders: pruritus, rash, urticaria, Stevens-Johnson syndrome/toxic epidermal necrolysis *[see Warnings and Precautions (5.2)]*.

Immune system disorders: hypersensitivity reactions including anaphylaxis and anaphylactic shock *[see Contraindications (4), Warnings and Precautions (5.2)]*.

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

Reference ID: 4239669

7 DRUG INTERACTIONS

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

When administered intravenously, fosaprepitant, a prodrug of aprepitant, is converted to aprepitant within 30 minutes. Therefore, drug interactions following administration of EMEND for injection are likely to occur with drugs that interact with oral aprepitant.

Fosaprepitant, given as a single 150-mg dose, is a weak inhibitor of CYP3A4, and the weak inhibition of CYP3A4 continues for 2 days after single dose administration. Single dose fosaprepitant does not induce CYP3A4. Aprepitant is a substrate, an inhibitor, and an inducer of CYP3A4. Aprepitant is also an inducer of CYP2C9 *[see Clinical Pharmacology (12.3)]*.

Some substrates of CYP3A4 are contraindicated with EMEND *[see Contraindications (4)]*. Dosage adjustment of some CYP3A4 and CYP2C9 substrates may be warranted, as shown in Table 5.

Table 5
Effects of Fosaprepitant/Aprepitant on the Pharmacokinetics of Other Drugs

CYP3A4 Substrates	
Pimozide	
Clinical Impact	Increased pimozide exposure
Intervention	EMEND is contraindicated *[see Contraindications (4)]*.
Benzodiazepines	
Clinical Impact	Increased exposure to midazolam or other benzodiazepines metabolized via CYP3A4 (alprazolam, triazolam) may increase the risk of adverse reactions *[see Clinical Pharmacology (12.3)]*.
Intervention	Monitor for benzodiazepine-related adverse reactions.
Dexamethasone	
Clinical Impact	Increased dexamethasone exposure *[see Clinical Pharmacology (12.3)]*.
Intervention	Reduce the dose of oral dexamethasone by approximately 50% *[see Dosage and Administration (2.1)]*.
Methylprednisolone	
Clinical Impact	Increased methylprednisolone exposure *[see Clinical Pharmacology (12.3)]*.
Intervention	Reduce the dose of oral methylprednisolone by approximately 50% on Days 1 and 2 for patients receiving HEC and on Day 1 for patients receiving MEC. Reduce the dose of intravenous methylprednisolone by 25% on Days 1 and 2 for patients receiving HEC and on Day 1 for patients receiving MEC.
Chemotherapeutic agents that are metabolized by CYP3A4	
Clinical Impact	Increased exposure of the chemotherapeutic agent may increase the risk of adverse reactions *[see Clinical Pharmacology (12.3)]*.
Intervention	Vinblastine, vincristine, or ifosfamide or other chemotherapeutic agents • Monitor for chemotherapeutic-related adverse reactions. Etoposide, vinorelbine, paclitaxel, and docetaxel • No dosage adjustment needed.
Hormonal Contraceptives	
Clinical Impact	Decreased hormonal exposure during administration of and for 28 days after administration of the last dose of EMEND *[see Warnings and Precautions (5.5), Use in Specific Populations (8.3), and Clinical Pharmacology (12.3)]*.
Intervention	Effective alternative or back-up methods of contraception (such as condoms and spermicides) should be used during treatment with EMEND and for 1 month following administration of EMEND.
Examples	birth control pills, skin patches, implants, and certain IUDs
CYP2C9 Substrates	
Warfarin	
Clinical Impact	Decreased warfarin exposure and prolongation of prothrombin time (INR) *[see Warnings and Precautions (5.4), Clinical Pharmacology (12.3)]*.
Intervention	In patients on chronic warfarin therapy, monitor the prothrombin time (INR) in the 2-week period, particularly at 7 to 10 days, following administration of EMEND with each chemotherapy cycle.
Other	
5-HT_3 Antagonists	
Clinical Impact	No change in the exposure of the 5-HT_3 antagonist *[see Clinical Pharmacology (12.3)]*.
Intervention	No dosage adjustment needed
Examples	ondansetron, granisetron, dolasetron

7.2 Effect of Other Drugs on the Pharmacokinetics of Fosaprepitant/Aprepitant

Aprepitant is a CYP3A4 substrate *[see Clinical Pharmacology (12.3)]*. Co-administration of EMEND with drugs that are inhibitors or inducers of CYP3A4 may result in increased or decreased plasma concentrations of aprepitant, respectively, as shown in Table 6.

Reference ID: 4239669

Table 6
Effects of Other Drugs on Pharmacokinetics of Fosaprepitant/Aprepitant

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are insufficient data on use of EMEND in pregnant women to inform a drug associated risk. In animal reproduction studies, no adverse developmental effects were observed in rats or rabbits exposed during the period of organogenesis to systemic drug levels (AUC) approximately equivalent to the exposure at the recommended human dose (RHD) of 150 mg *[see Data]*.

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

Data

Animal Data

In embryofetal development studies in rats and rabbits, aprepitant was administered during the period of organogenesis at oral doses up to 1000 mg/kg twice daily (rats) and up to the maximum tolerated dose of 25 mg/kg/day (rabbits). No embryofetal lethality or malformations were observed at any dose level in either species. The exposures (AUC) in pregnant rats at 1000 mg/kg twice daily and in pregnant rabbits at 125 mg/kg/day were approximately equivalent to the exposure at the RHD of 150 mg. Aprepitant crosses the placenta in rats and rabbits.

8.2 Lactation

Risk Summary

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

8.3 Females and Males of Reproductive Potential

Contraception

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

8.4 Pediatric Use

The safety and effectiveness of EMEND for injection have not been established in pediatric patients.

Reference ID: 4239669

8.5 Geriatric Use

Of the 1649 adult cancer patients treated with intravenous EMEND in HEC and MEC clinical studies, 27% were aged 65 and over, while 5% were aged 75 and over. Other reported clinical experience with EMEND has not identified differences in responses between elderly and younger patients. In general, use caution when dosing elderly patients as they have a greater frequency of decreased hepatic, renal or cardiac function and concomitant disease or other drug therapy *[see Clinical Pharmacology (12.3)]*.

8.6 Patients with Hepatic Impairment

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

10 OVERDOSAGE

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

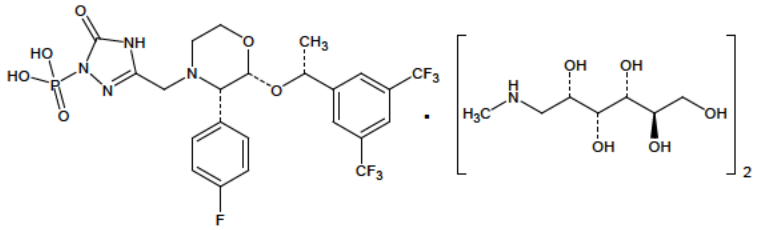
In the event of overdose, EMEND should be discontinued and general supportive treatment and monitoring should be provided. Because of the antiemetic activity of EMEND, drug-induced emesis may not be effective in cases of EMEND overdosage.

Aprepitant is not removed by hemodialysis.

11 DESCRIPTION

EMEND (fosaprepitant) for injection is a sterile, lyophilized formulation containing fosaprepitant dimeglumine, a prodrug of aprepitant, a substance P/neurokinin-1 (NK_1) receptor antagonist, an antiemetic agent, 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.

Each vial of EMEND for injection for administration as an intravenous infusion contains 150 mg of fosaprepitant (equivalent to 245.3 mg of fosaprepitant dimeglumine) and the following inactive ingredients: edetate disodium (5.4 mg), polysorbate 80 (75 mg), lactose anhydrous (375 mg), sodium hydroxide and/or hydrochloric acid (for pH adjustment).

12 CLINICAL PHARMACOLOGY

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 ($5\text{-}HT_3$), 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

Reference ID: 4239669

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

Cardiac Electrophysiology

In a randomized, double-blind, positive-controlled, thorough QTc study, a single 200-mg dose of fosaprepitant (approximately 1.3 times the recommended dose) had no effect on the QTc interval.

12.3 Pharmacokinetics

Aprepitant after Fosaprepitant Administration

Following administration of a single intravenous 150-mg dose of fosaprepitant, a prodrug of aprepitant administered as a 20-minute infusion to healthy subjects, the mean $AUC_{0-\infty}$ of aprepitant was 37.4 (± 14.8) mcg•hr/mL and the mean maximal aprepitant concentration (C_{max}) was 4.2 (± 1.2) mcg/mL. Plasma concentrations of fosaprepitant are below the limits of quantification (10 ng/mL) within 30 minutes of the completion of infusion.

Distribution

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

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

Elimination

Metabolism

Fosaprepitant is converted to aprepitant in *in vitro* incubations with human liver preparations and 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.

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

Age: Geriatric Population

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_{0-24hr} of aprepitant was 21% higher on Day 1 and 36% higher on Day 5 in elderly (65 years and older) relative to younger adults. The C_{max} was 10% higher on Day 1 and 24% higher on Day 5 in elderly relative to younger adults. These differences are not considered clinically meaningful *[see Use in Specific Populations (8.5)]*.

Sex

Following oral administration of a single dose of aprepitant, ranging from 40 mg to 375 mg, the AUC_{0-24hr} and C_{max} are 9% and 17% higher in females as compared with males. The half-life of aprepitant

Reference ID: 4239669

is approximately 25% lower in females as compared with males and T_{max} occurs at approximately the same time. These differences are not considered clinically meaningful.

Race/Ethnicity

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

Renal Impairment

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

In patients with severe renal impairment, the $AUC_{0-\infty}$ of total aprepitant (unbound and protein bound) decreased by 21% and C_{max} decreased by 32%, relative to healthy subjects (creatinine clearance greater than 80 mL/min estimated by Cockcroft-Gault method). In patients with ESRD undergoing hemodialysis, the $AUC_{0-\infty}$ of total aprepitant decreased by 42% and C_{max} decreased by 32%. Due to modest decreases in protein binding of aprepitant in patients with renal disease, the AUC of pharmacologically active unbound drug was not significantly affected in patients with renal impairment compared with healthy subjects. Hemodialysis conducted 4 or 48 hours after dosing had no significant effect on the pharmacokinetics of aprepitant; less than 0.2% of the dose was recovered in the dialysate.

Hepatic Impairment

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 oral dose of 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_{0-24hr} of aprepitant was 11% lower on Day 1 and 36% lower on Day 3, as compared with healthy subjects given the same regimen. In patients with moderate hepatic impairment (Child-Pugh score 7 to 9), the AUC_{0-24hr} of aprepitant was 10% higher on Day 1 and 18% higher on Day 3, as compared with healthy subjects given the same regimen. These differences in AUC_{0-24hr} are not considered clinically meaningful. There are no clinical or pharmacokinetic data in patients with severe hepatic impairment (Child-Pugh score greater than 9) *[see Use in Specific Populations (8.6)]*.

Body Mass Index (BMI)

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

<u>Drug Interactions Studies</u>

Fosaprepitant, given as a single 150-mg dose, is a weak inhibitor of CYP3A4, with no evidence of inhibition or induction of CYP3A4 observed on Day 4. The weak inhibition of CYP3A4 continues for 2 days after single dose administration of fosaprepitant. Aprepitant is a substrate, an inhibitor, and an inducer of CYP3A4. Aprepitant is also an inducer of CYP2C9.

Fosaprepitant or aprepitant is unlikely to interact with drugs that are substrates for the P-glycoprotein transporter.

<u>Effects of Fosaprepitant/Aprepitant on the Pharmacokinetics of Other Drugs</u>

CYP3A4 Substrates

Midazolam: Fosaprepitant 150 mg administered as a single intravenous dose on Day 1 increased the $AUC_{0-\infty}$ of midazolam by approximately 1.8-fold on Day 1 and had no effect on Day 4 when midazolam was coadministered as a single oral dose of 2 mg on Days 1 and 4 *[see Drug Interactions (7.1)]*.

Corticosteroids:

Reference ID: 4239669

Dexamethasone: Fosaprepitant administered as a single 150 mg 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 *[see Dosage and Administration (2.1), Drug Interactions (7.1)]*.

Methylprednisolone: When oral aprepitant as a 3-day regimen (125-mg/80-mg/80-mg) was administered with intravenous methylprednisolone 125 mg on Day 1 and oral methylprednisolone 40 mg on Days 2 and 3, the AUC of methylprednisolone was increased by 1.34-fold on Day 1 and by 2.5-fold on Day 3 *[see Drug Interactions (7.1)]*.

Chemotherapeutic agents:
Docetaxel: In a pharmacokinetic study, oral aprepitant administered as a 3-day regimen (125-mg/80-mg/80-mg) did not influence the pharmacokinetics of docetaxel.

Vinorelbine: In a pharmacokinetic study, oral aprepitant administered as a 3-day regimen (125-mg/80-mg/80-mg) did not influence the pharmacokinetics of vinorelbine to a clinically significant degree.

Oral contraceptives: When oral aprepitant was administered as a 3-day regimen (125-mg/80-mg/80-mg) with ondansetron and dexamethasone, and coadministered with an oral contraceptive containing ethinyl estradiol and norethindrone, the trough concentrations of both ethinyl estradiol and norethindrone were reduced by as much as 64% for 3 weeks post-treatment *[see Drug Interactions (7.1)]*.

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 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 *[see Drug Interactions (7.1)]*.

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 prior to the administration of the 3-day regimen of oral aprepitant and on Days 4, 8, and 15. This effect was not considered clinically important.

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

5-HT_3 antagonists: In clinical drug interaction studies, aprepitant did not have clinically important effects on the pharmacokinetics of ondansetron, granisetron, or hydrodolasetron (the active metabolite of dolasetron).

<u>Effect of Other Drugs on the Pharmacokinetics of Fosaprepitant/Aprepitant</u>
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 *[see Drug Interactions (7.2)]*.

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 *[see Drug Interactions (7.2)]*.

Diltiazem: In a study in 10 patients with mild to moderate hypertension, administration of 100 mg of fosaprepitant as an intravenous infusion with 120 mg of diltiazem, a moderate CYP3A4 inhibitor

administered three times daily, resulted in a 1.5-fold increase in the aprepitant AUC and a 1.4-fold increase in the diltiazem AUC.

When fosaprepitant was administered with diltiazem, the mean maximum decrease in diastolic blood pressure was significantly greater than that observed with diltiazem alone [24.3 ± 10.2 mm Hg with fosaprepitant versus 15.6 ± 4.1 mm Hg without fosaprepitant]. The mean maximum decrease in systolic blood pressure was also greater after co-administration of diltiazem with fosaprepitant than administration of diltiazem alone [29.5 ± 7.9 mm Hg with fosaprepitant versus 23.8 ± 4.8 mm Hg without fosaprepitant]. Co-administration of fosaprepitant and diltiazem; however, did not result in any additional clinically significant changes in heart rate or PR interval, beyond those changes observed with diltiazem alone *[see Drug Interactions (7.2)]*.

Paroxetine: Coadministration of once daily doses of oral aprepitant 170 mg, with paroxetine 20 mg once daily, resulted in a decrease in AUC by approximately 25% and C_{max} by approximately 20% of both aprepitant and paroxetine. This effect was not considered clinically important.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies were conducted in Sprague-Dawley rats and in CD-1 mice for 2 years. In the rat carcinogenicity studies, animals were treated with oral doses ranging from 0.05 to 1000 mg/kg twice daily. The highest dose produced systemic exposures to aprepitant approximately equivalent to (female rats) or less than (male rats) the human exposure at the RHD of 150 mg. 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 approximately 2 times the human exposure at the RHD of 150 mg. Treatment with aprepitant produced skin fibrosarcomas at 125 and 500 mg/kg/day doses in male mice. Carcinogenicity studies were not conducted with fosaprepitant.

Mutagenesis

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.

Impairment of Fertility

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 RHD of 150 mg and exposure in female rats approximately equivalent to the human exposure).

14 CLINICAL STUDIES

14.1 Prevention of Nausea and Vomiting Associated with HEC

In a randomized, parallel, double-blind, active-controlled study, EMEND for injection 150 mg as a single intravenous infusion (N=1147) was compared to a 3-day oral EMEND regimen (N=1175) in patients receiving a HEC regimen that included cisplatin (≥70 mg/m^2). All patients in both groups received dexamethasone and ondansetron (see Table 7). Patient demographics were similar between the two treatment groups. Of the total 2322 patients, 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 commonly administered were fluorouracil (17%), gemcitabine (16%), paclitaxel (15%), and etoposide (12%).

Table 7
Treatment Regimens in HEC Trial*

	Day 1	Day 2	Day 3	Day 4
EMEND Regimen				
EMEND for injection	150 mg intravenously over 20 to 30 minutes approximately 30 minutes prior to chemotherapy	none	none	none
Oral dexamethasone†	12 mg	8 mg	8 mg twice daily	8 mg twice daily
Ondansetron	Ondansetron‡	none	none	none
Oral EMEND Regimen				
EMEND capsules	125 mg	80 mg	80 mg	none
Oral dexamethasone§	12 mg	8 mg	8 mg	8 mg
Ondansetron	Ondansetron‡	none	none	none

*EMEND for injection placebo, EMEND capsules placebo and dexamethasone placebo (in the evenings on Days 3 and 4) were used to maintain blinding.

†Dexamethasone was administered 30 minutes prior to chemotherapy treatment on Day 1 and in the morning on Days 2 through 4. Dexamethasone was also administered in the evenings on Days 3 and 4. The 12 mg dose of dexamethasone on Day 1 and the 8 mg once daily dose on Day 2 reflects a dosage adjustment to account for a drug interaction with the EMEND for injection regimen *[see Clinical Pharmacology (12.3)].*

‡Ondansetron 32 mg intravenous was used in the clinical trials of EMEND. Although this dose was used in clinical trials, this is no longer the currently recommended dose. Refer to the ondansetron prescribing information for the current recommended dose.

§Dexamethasone was administered 30 minutes prior to chemotherapy treatment on Day 1 and in the morning on Days 2 through 4. The 12 mg dose of dexamethasone on Day 1 and the 8 mg once daily dose on Days 2 through 4 reflects a dosage adjustment to account for a drug interaction with the oral EMEND regimen *[see Clinical Pharmacology (12.3)].*

The efficacy of EMEND for injection was evaluated based on the primary and secondary endpoints listed in Table 8 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%.

Reference ID: 4239669

Table 8
Percent of Patients Receiving Highly Emetogenic Chemotherapy Responding by Treatment Group and Phase — Cycle 1

ENDPOINTS	EMEND for Injection Regimen (N = 1106)* %	Oral EMEND 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 Prevention of Nausea and Vomiting Associated with MEC

In a randomized, parallel, double-blind, active comparator-controlled study, EMEND for injection 150 mg as a single intravenous infusion (N=502) in combination with ondansetron and dexamethasone (EMEND regimen) was compared with ondansetron and dexamethasone alone (standard therapy) (N=498) (see Table 9) in patients receiving a MEC regimen. Patient demographics were similar between the two treatment groups. Of the total 1,000 patients included in the efficacy analysis, 41% were men, 84% White, 4% Asian, 1% American Indian/Alaska Native, 2% Black, 10% Multi-Racial, and 19% Hispanic/Latino ethnicity. Patient ages ranged from 23 to 88 years of age, with a mean age of 60 years. The most commonly administered MEC chemotherapeutic agents were carboplatin (51%), oxaliplatin (24%), and cyclophosphamide (12%).

Table 9
Treatment Regimens in MEC Trial*

	Day 1	Day 2	Day 3
EMEND Regimen			
EMEND for Injection	150 mg intravenously over 20 to 30 minutes approximately 30 minutes prior to chemotherapy	none	none
Oral Dexamethasone[†]	12 mg	none	none
Oral Ondansetron[‡]	8 mg for 2 doses	none	none
Standard Therapy			
Oral Dexamethasone	20 mg	none	none
Oral Ondansetron[‡]	8 mg for 2 doses	8 mg twice daily	8 mg twice daily

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

Reference ID: 4239669

The primary endpoint was complete response (defined as no vomiting and no rescue therapy) in the delayed phase (25 to 120 hours) of chemotherapy-induced nausea and vomiting. The results by treatment group are shown in Table 10.

Table 10
Percent of Patients Receiving Moderately Emetogenic Chemotherapy Responding by Treatment Group

ENDPOINTS	EMEND for Injection Regimen (N = 502)* %	Standard Therapy Regimen (N = 498)* %	P-Value	Treatment Difference (95% CI)
PRIMARY ENDPOINT				
Complete Response†				
Delayed phase‡	78.9	68.5	<0.001	10.4 (5.1, 15.9)

*N: Number of patients included in the intention to treat population.
†Complete Response = no vomiting and no use of rescue therapy.
‡Delayed phase = 25 to 120 hours post-initiation of chemotherapy.

16 HOW SUPPLIED/STORAGE AND HANDLING

No. 3061 — Single-dose glass vial containing 150 mg of fosaprepitant as a white to off-white lyophilized powder for reconstitution. Supplied as follows:

NDC 0006-3061-00 1 vial per carton.

Storage

Emend for injection vials must be refrigerated, store at 2°C-8°C (36°F-46°F).

The reconstituted final drug solution is stable for 24 hours at ambient room temperature [at or below 25°C (77°F)].

17 PATIENT COUNSELING INFORMATION

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

Hypersensitivity

Advise patients that hypersensitivity reactions, including anaphylaxis and anaphylactic shock, have been reported in patients taking EMEND. Advise patients to seek immediate medical attention if they experience signs or symptoms of a hypersensitivity reaction, such as hives, rash and itching, skin peeling or sores, flushing, difficulty in breathing or swallowing, or dizziness, rapid or weak heartbeat or feeling faint *[see Warnings and Precautions (5.2)]*.

Infusion Site Reactions

Advise patients to seek medical attention if they experience new or worsening signs or symptoms of an infusion site reaction, such as erythema, edema, pain, necrosis, vasculitis, or thrombophlebitis at or near the infusion site *[see Warnings and Precautions (5.3)]*.

Drug Interactions

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

Warfarin: Instruct patients on chronic warfarin therapy to follow instructions from their healthcare provider regarding blood draws to monitor their INR during the 2-week period, particularly at 7 to 10 days, following initiation of EMEND with each chemotherapy cycle *[see Warnings and Precautions (5.4)]*.

Hormonal Contraceptives: Advise patients that administration of EMEND may reduce the efficacy of hormonal contraceptives. Instruct patients to use effective alternative or back-up methods of contraception (such as condoms and spermicides) during treatment with EMEND and for 1 month following administration of EMEND *[see Warnings and Precautions (5.5), Use in Specific Populations (8.3)]*.

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

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

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

----------RECENT MAJOR CHANGES----------

Warnings and Precautions (5.2)	08/2017
Warnings and Precautions (5.3)	03/2018

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

EMEND® for injection is a substance P/neurokinin-1 (NK_1) receptor antagonist, indicated in adults, in combination with other antiemetic agents, for the prevention of (1):

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

Limitations of Use (1)

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

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

Dosage (2.1)

- Recommended dosage in adults is 150 mg on Day 1 as an intravenous infusion over 20 to 30 minutes approximately 30 minutes prior to chemotherapy.
- See Full Prescribing Information for recommended dosages of concomitant dexamethasone and a 5-HT_3 antagonist for HEC and MEC.

Preparation (2.2)

- Reconstitute with 5 mL of 0.9% sodium chloride.
- Add to infusion bag containing 145 mL 0.9% sodium chloride for a final concentration of 1 mg/mL.

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

EMEND for injection: 150 mg fosaprepitant, lyophilized powder in single-dose vial for reconstitution. (3)

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

- Known hypersensitivity to any component of this drug. (4, 5.2)
- Concurrent use with pimozide. (4)

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

- CYP3A4 Interactions: Fosaprepitant is a weak inhibitor of CYP3A4, and aprepitant, the active moiety, is a substrate, inhibitor, and inducer of CYP3A4; see Full Prescribing Information for recommendations regarding contraindications, risk of adverse reactions, and dosage adjustment of EMEND and concomitant drugs. (4, 5.1, 7.1, 7.2)
- Hypersensitivity Reactions (including anaphylaxis and anaphylactic shock): May occur during or soon after infusion. If symptoms occur, discontinue the drug. Do not reinitiate EMEND if symptoms occur with first-time use. (4, 5.2)
- Infusion Site Reactions (including thrombophlebitis, necrosis, and vasculitis): Majority of reactions reported in patients receiving vesicant chemotherapy. Avoid infusion into small veins. Discontinue infusion and administer treatment if a severe reaction develops. (5.3)
- Warfarin (a CYP2C9 substrate): Risk of decreased INR of prothrombin time; monitor INR in 2–week period, particularly at 7 to 10 days, following initiation of EMEND. (5.4, 7.1)
- Hormonal Contraceptives: Efficacy of contraceptives may be reduced during and for 28 days following administration of EMEND. Use effective alternative or back-up methods of contraception. (5.5, 7.1, 8.3)

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

Most common adverse reactions (≥2%) are: fatigue, diarrhea, neutropenia, asthenia, anemia, peripheral neuropathy, leukopenia, dyspepsia, urinary tract infection, pain in extremity. (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----------

See Full Prescribing Information for a list of clinically significant drug interactions. (4, 5.1, 5.4, 5.5, 7.1, 7.2)

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

Revised: 03/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Prevention of Nausea and Vomiting Associated with HEC and MEC
2.2 Preparation of EMEND for Injection
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Clinically Significant CYP3A4 Drug Interactions
5.2 Hypersensitivity Reactions
5.3 Infusion Site Reactions
5.4 Decrease in INR with Concomitant Warfarin
5.5 Risk of Reduced Efficacy of Hormonal Contraceptives
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Postmarketing Experience
7 DRUG INTERACTIONS
7.1 Effect of Fosaprepitant/Aprepitant on the Pharmacokinetics of Other Drugs
7.2 Effect of Other Drugs on the Pharmacokinetics of Fosaprepitant/Aprepitant
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.3 Females and Males of Reproductive Potential
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Patients with Hepatic Impairment
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
14.1 Prevention of Nausea and Vomiting Associated with HEC
14.2 Prevention of Nausea and Vomiting Associated with MEC
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

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

Reference ID: 4239669

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

EMEND® for injection, in combination with other antiemetic agents, is indicated in adults 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.
- delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC).

Limitations of Use

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

2 DOSAGE AND ADMINISTRATION

2.1 Prevention of Nausea and Vomiting Associated with HEC and MEC

The recommended dosage of EMEND for injection, dexamethasone, and a 5-HT_3 antagonist in adults for the prevention of nausea and vomiting associated with administration of HEC or MEC is shown in Table 1 or Table 2, respectively. Administer EMEND for injection as an intravenous infusion on Day 1 over 20 to 30 minutes approximately 30 minutes prior to chemotherapy.

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

	Day 1	Day 2	Day 3	Day 4
EMEND for injection	150 mg intravenously over 20 to 30 minutes approximately 30 minutes prior to chemotherapy	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 selected 5-HT_3 antagonist prescribing information for the recommended dosage	none	none	none

*Administer dexamethasone 30 minutes prior to chemotherapy treatment on Day 1 and in the morning on Days 2 through 4. Also administer dexamethasone in the evenings on Days 3 and 4. A 50% dosage reduction of dexamethasone on Days 1 and 2 is recommended to account for a drug interaction with EMEND *[see Clinical Pharmacology (12.3)]*.

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

	Day 1
EMEND for injection	150 mg intravenously over 20 to 30 minutes approximately 30 minutes prior to chemotherapy
Dexamethasone*	12 mg orally
5-HT_3 antagonist	See selected 5-HT_3 antagonist prescribing information for the recommended dosage

*Administer dexamethasone 30 minutes prior to chemotherapy treatment on Day 1. A 50% dosage reduction of dexamethasone is recommended to account for a drug interaction with EMEND *[see Clinical Pharmacology (12.3)]*.

Reference ID: 4239669

2.2 Preparation of EMEND for Injection

Table 3
Preparation Instructions for EMEND for Injection

Step 1	Aseptically inject 5 mL 0.9% Sodium Chloride Injection, USP into the vial. Assure that 0.9% Sodium Chloride Injection, USP is added to the vial along the vial wall in order to prevent foaming. Swirl the vial gently. Avoid shaking and jetting 0.9% Sodium Chloride Injection, USP into the vial.
Step 2	Aseptically prepare an infusion bag filled with **145 mL** of 0.9% Sodium Chloride Injection, USP.
Step 3	Aseptically withdraw the entire volume from the vial and transfer it into the infusion bag containing **145 mL** of 0.9% Sodium Chloride Injection, USP to yield a total volume of **150 mL** and a final concentration of 1 mg/mL**.**
Step 4	Gently invert the bag 2 to 3 times.
Step 5	Before administration, inspect the bag for particulate matter and discoloration. Discard the bag if particulate and/or discoloration are observed.

Caution: Do not mix or reconstitute EMEND for injection 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.

Storage

The reconstituted final drug solution is stable for 24 hours at ambient room temperature [at or below 25°C (77°F)].

3 DOSAGE FORMS AND STRENGTHS

EMEND for injection: 150 mg fosaprepitant, white to off-white lyophilized powder in single-dose glass vial for reconstitution

4 CONTRAINDICATIONS

EMEND is contraindicated in patients:

- who are hypersensitive to any component of the product. Hypersensitivity reactions including anaphylactic reactions, flushing, erythema, and dyspnea have been reported *[see Warnings and Precautions (5.2), Adverse Reactions (6.2)]*.

- taking pimozide. Inhibition of CYP3A4 by aprepitant, the active moiety, could result in elevated plasma concentrations of this drug, which is a CYP3A4 substrate, potentially causing serious or life-threatening reactions, such as QT prolongation, a known adverse reaction of pimozide *[see Warnings and Precautions (5.1)].*

5 WARNINGS AND PRECAUTIONS

5.1 Clinically Significant CYP3A4 Drug Interactions

Fosaprepitant, a prodrug of aprepitant, is a weak inhibitor of CYP3A4, and aprepitant is a substrate, inhibitor, and inducer of CYP3A4.

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

See Table 5 and Table 6 for a listing of potentially significant drug interactions *[see Drug Interactions (7.1, 7.2)].*

5.2 Hypersensitivity Reactions

Serious hypersensitivity reactions, including anaphylaxis and anaphylactic shock, during or soon after infusion of fosaprepitant have occurred. Symptoms including flushing, erythema, dyspnea, hypotension and syncope have been reported *[see Adverse Reactions (6.2)]*.

Monitor patients during and after infusion. If hypersensitivity reactions occur, discontinue the infusion and administer appropriate medical therapy. Do not reinitiate EMEND in patients who experience these symptoms with first-time use *[see Contraindications (4)]*.

5.3 Infusion Site Reactions

Infusion site reactions (ISRs) have been reported with the use of EMEND for injection *[see Adverse Reactions (6.1)]*. The majority of severe ISRs, including thrombophlebitis and vasculitis, were reported with concomitant vesicant (anthracycline-based) chemotherapy administration, particularly when associated with extravasation. Necrosis was also reported in some patients with concomitant vesicant chemotherapy. Most ISRs occurred with the first, second or third exposure to single doses of EMEND for injection and in some cases, reactions persisted for two weeks or longer. Treatment of severe ISRs consisted of medical, and in some cases surgical, intervention.

Avoid infusion of EMEND for injection into small veins or through a butterfly catheter. If a severe ISR develops during infusion, discontinue the infusion and administer appropriate medical treatment.

5.4 Decrease in INR with Concomitant Warfarin

Coadministration of EMEND with warfarin, a CYP2C9 substrate, may result in a clinically significant decrease in the International Normalized Ratio (INR) of prothrombin time *[see Clinical Pharmacology (12.3)]*. Monitor the INR in patients on chronic warfarin therapy in the 2-week period, particularly at 7 to 10 days, following initiation of EMEND with each chemotherapy cycle *[see Drug Interactions (7.1)]*.

5.5 Risk of Reduced Efficacy of Hormonal Contraceptives

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

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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

The overall safety of EMEND for injection was evaluated in approximately 1600 individuals.

<u>Adverse Reactions for the Prevention of Nausea and Vomiting Associated with MEC</u>

Reference ID: 4239669

In an active-controlled clinical trial in patients receiving MEC, safety was evaluated in 504 patients receiving a single dose of EMEND for injection in combination with ondansetron and dexamethasone (EMEND regimen) compared to 497 patients receiving ondansetron and dexamethasone alone (standard therapy). The most common adverse reactions are listed in Table 4.

Table 4
Most Common Adverse Reactions in Patients Receiving MEC*

	EMEND for injection, ondansetron, and dexamethasone† (N=504)	**Ondansetron and dexamethasone‡ (N=497)**
fatigue	15%	13%
diarrhea	13%	11%
neutropenia	8%	7%
asthenia	4%	3%
anemia	3%	2%
peripheral neuropathy	3%	2%
leukopenia	2%	1%
dyspepsia	2%	1%
urinary tract infection	2%	1%
pain in extremity	2%	1%

*Reported in ≥ 2% of patients treated with the EMEND regimen and at a greater incidence than standard therapy.
†EMEND regimen
‡Standard therapy

Infusion-site reactions were reported in 2.2% of patients treated with the EMEND regimen compared to 0.6% of patients treated with standard therapy. The infusion-site reactions included: infusion-site pain (1.2%, 0.4%), injection-site irritation (0.2%, 0.0%), vessel puncture-site pain (0.2%, 0.0%), and infusion-site thrombophlebitis (0.6%, 0.0%), reported in the EMEND regimen compared to standard therapy, respectively.

Adverse Reactions for the Prevention of Nausea and Vomiting Associated with HEC

In an active-controlled clinical study in patients receiving HEC, safety was evaluated for 1143 patients receiving a single dose of EMEND for injection compared to 1169 patients receiving the 3-day regimen of oral EMEND (aprepitant) *[see Clinical Studies (14.1)]*. The safety profile was generally similar to that seen in the MEC study with fosaprepitant and 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 following additional infusion-site reactions occurred in the HEC study and were not reported in the MEC study described above: infusion-site erythema (0.5%, 0.1%), infusion-site pruritus (0.3%, 0.0%), and infusion-site induration (0.2%, 0.1%), reported in the fosaprepitant group compared to the aprepitant group, respectively.

Since fosaprepitant is converted to aprepitant, those adverse reactions associated with aprepitant might also be expected to occur with EMEND for injection. See the full prescribing information for EMEND capsules for complete safety information regarding studies performed with oral aprepitant.

6.2 Postmarketing Experience

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

Skin and subcutaneous tissue disorders: pruritus, rash, urticaria, Stevens-Johnson syndrome/toxic epidermal necrolysis *[see Warnings and Precautions (5.2)]*.

Immune system disorders: hypersensitivity reactions including anaphylaxis and anaphylactic shock *[see Contraindications (4), Warnings and Precautions (5.2)]*.

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

Reference ID: 4239669

7 DRUG INTERACTIONS

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

When administered intravenously, fosaprepitant, a prodrug of aprepitant, is converted to aprepitant within 30 minutes. Therefore, drug interactions following administration of EMEND for injection are likely to occur with drugs that interact with oral aprepitant.

Fosaprepitant, given as a single 150-mg dose, is a weak inhibitor of CYP3A4, and the weak inhibition of CYP3A4 continues for 2 days after single dose administration. Single dose fosaprepitant does not induce CYP3A4. Aprepitant is a substrate, an inhibitor, and an inducer of CYP3A4. Aprepitant is also an inducer of CYP2C9 *[see Clinical Pharmacology (12.3)]*.

Some substrates of CYP3A4 are contraindicated with EMEND *[see Contraindications (4)]*. Dosage adjustment of some CYP3A4 and CYP2C9 substrates may be warranted, as shown in Table 5.

Table 5
Effects of Fosaprepitant/Aprepitant on the Pharmacokinetics of Other Drugs

CYP3A4 Substrates	
Pimozide	
Clinical Impact	Increased pimozide exposure
Intervention	EMEND is contraindicated *[see Contraindications (4)]*.
Benzodiazepines	
Clinical Impact	Increased exposure to midazolam or other benzodiazepines metabolized via CYP3A4 (alprazolam, triazolam) may increase the risk of adverse reactions *[see Clinical Pharmacology (12.3)]*.
Intervention	Monitor for benzodiazepine-related adverse reactions.
Dexamethasone	
Clinical Impact	Increased dexamethasone exposure *[see Clinical Pharmacology (12.3)]*.
Intervention	Reduce the dose of oral dexamethasone by approximately 50% *[see Dosage and Administration (2.1)]*.
Methylprednisolone	
Clinical Impact	Increased methylprednisolone exposure *[see Clinical Pharmacology (12.3)]*.
Intervention	Reduce the dose of oral methylprednisolone by approximately 50% on Days 1 and 2 for patients receiving HEC and on Day 1 for patients receiving MEC. Reduce the dose of intravenous methylprednisolone by 25% on Days 1 and 2 for patients receiving HEC and on Day 1 for patients receiving MEC.
Chemotherapeutic agents that are metabolized by CYP3A4	
Clinical Impact	Increased exposure of the chemotherapeutic agent may increase the risk of adverse reactions *[see Clinical Pharmacology (12.3)]*.
Intervention	<u>Vinblastine, vincristine, or ifosfamide or other chemotherapeutic agents</u> • Monitor for chemotherapeutic-related adverse reactions. <u>Etoposide, vinorelbine, paclitaxel, and docetaxel</u> • No dosage adjustment needed.
Hormonal Contraceptives	
Clinical Impact	Decreased hormonal exposure during administration of and for 28 days after administration of the last dose of EMEND *[see Warnings and Precautions (5.5), Use in Specific Populations (8.3), and Clinical Pharmacology (12.3)]*.
Intervention	Effective alternative or back-up methods of contraception (such as condoms and spermicides) should be used during treatment with EMEND and for 1 month following administration of EMEND.
Examples	birth control pills, skin patches, implants, and certain IUDs
CYP2C9 Substrates	
Warfarin	
Clinical Impact	Decreased warfarin exposure and prolongation of prothrombin time (INR) *[see Warnings and Precautions (5.4), Clinical Pharmacology (12.3)]*.
Intervention	In patients on chronic warfarin therapy, monitor the prothrombin time (INR) in the 2-week period, particularly at 7 to 10 days, following administration of EMEND with each chemotherapy cycle.
Other	
5-HT_3 Antagonists	
Clinical Impact	No change in the exposure of the 5-HT_3 antagonist *[see Clinical Pharmacology (12.3)]*.
Intervention	No dosage adjustment needed
Examples	ondansetron, granisetron, dolasetron

7.2 Effect of Other Drugs on the Pharmacokinetics of Fosaprepitant/Aprepitant

Aprepitant is a CYP3A4 substrate *[see Clinical Pharmacology (12.3)]*. Co-administration of EMEND with drugs that are inhibitors or inducers of CYP3A4 may result in increased or decreased plasma concentrations of aprepitant, respectively, as shown in Table 6.

Reference ID: 4239669

Table 6
Effects of Other Drugs on Pharmacokinetics of Fosaprepitant/Aprepitant

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are insufficient data on use of EMEND in pregnant women to inform a drug associated risk. In animal reproduction studies, no adverse developmental effects were observed in rats or rabbits exposed during the period of organogenesis to systemic drug levels (AUC) approximately equivalent to the exposure at the recommended human dose (RHD) of 150 mg *[see Data]*.

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

Data

Animal Data

In embryofetal development studies in rats and rabbits, aprepitant was administered during the period of organogenesis at oral doses up to 1000 mg/kg twice daily (rats) and up to the maximum tolerated dose of 25 mg/kg/day (rabbits). No embryofetal lethality or malformations were observed at any dose level in either species. The exposures (AUC) in pregnant rats at 1000 mg/kg twice daily and in pregnant rabbits at 125 mg/kg/day were approximately equivalent to the exposure at the RHD of 150 mg. Aprepitant crosses the placenta in rats and rabbits.

8.2 Lactation

Risk Summary

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

8.3 Females and Males of Reproductive Potential

Contraception

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

8.4 Pediatric Use

The safety and effectiveness of EMEND for injection have not been established in pediatric patients.

Reference ID: 4239669

8.5 Geriatric Use

Of the 1649 adult cancer patients treated with intravenous EMEND in HEC and MEC clinical studies, 27% were aged 65 and over, while 5% were aged 75 and over. Other reported clinical experience with EMEND has not identified differences in responses between elderly and younger patients. In general, use caution when dosing elderly patients as they have a greater frequency of decreased hepatic, renal or cardiac function and concomitant disease or other drug therapy *[see Clinical Pharmacology (12.3)]*.

8.6 Patients with Hepatic Impairment

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

10 OVERDOSAGE

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

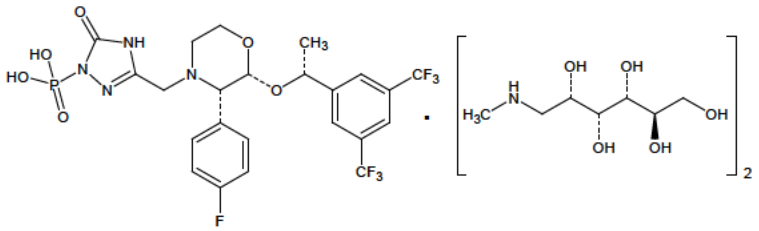
In the event of overdose, EMEND should be discontinued and general supportive treatment and monitoring should be provided. Because of the antiemetic activity of EMEND, drug-induced emesis may not be effective in cases of EMEND overdosage.

Aprepitant is not removed by hemodialysis.

11 DESCRIPTION

EMEND (fosaprepitant) for injection is a sterile, lyophilized formulation containing fosaprepitant dimeglumine, a prodrug of aprepitant, a substance P/neurokinin-1 (NK_1) receptor antagonist, an antiemetic agent, 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.

Each vial of EMEND for injection for administration as an intravenous infusion contains 150 mg of fosaprepitant (equivalent to 245.3 mg of fosaprepitant dimeglumine) 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).

12 CLINICAL PHARMACOLOGY

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

Reference ID: 4239669

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

Cardiac Electrophysiology

In a randomized, double-blind, positive-controlled, thorough QTc study, a single 200-mg dose of fosaprepitant (approximately 1.3 times the recommended dose) had no effect on the QTc interval.

12.3 Pharmacokinetics

Aprepitant after Fosaprepitant Administration

Following administration of a single intravenous 150-mg dose of fosaprepitant, a prodrug of aprepitant administered as a 20-minute infusion to healthy subjects, the mean $AUC_{0-\infty}$ of aprepitant was 37.4 (± 14.8) mcg•hr/mL and the mean maximal aprepitant concentration (C_{max}) was 4.2 (± 1.2) mcg/mL. Plasma concentrations of fosaprepitant are below the limits of quantification (10 ng/mL) within 30 minutes of the completion of infusion.

Distribution

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

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

Elimination

Metabolism

Fosaprepitant is converted to aprepitant in *in vitro* incubations with human liver preparations and 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.

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

Age: Geriatric Population

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_{0-24hr} of aprepitant was 21% higher on Day 1 and 36% higher on Day 5 in elderly (65 years and older) relative to younger adults. The C_{max} was 10% higher on Day 1 and 24% higher on Day 5 in elderly relative to younger adults. These differences are not considered clinically meaningful *[see Use in Specific Populations (8.5)]*.

Sex

Following oral administration of a single dose of aprepitant, ranging from 40 mg to 375 mg, the AUC_{0-24hr} and C_{max} are 9% and 17% higher in females as compared with males. The half-life of aprepitant

Reference ID: 4239669

is approximately 25% lower in females as compared with males and T_{max} occurs at approximately the same time. These differences are not considered clinically meaningful.

Race/Ethnicity

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

Renal Impairment

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

In patients with severe renal impairment, the $AUC_{0-\infty}$ of total aprepitant (unbound and protein bound) decreased by 21% and C_{max} decreased by 32%, relative to healthy subjects (creatinine clearance greater than 80 mL/min estimated by Cockcroft-Gault method). In patients with ESRD undergoing hemodialysis, the $AUC_{0-\infty}$ of total aprepitant decreased by 42% and C_{max} decreased by 32%. Due to modest decreases in protein binding of aprepitant in patients with renal disease, the AUC of pharmacologically active unbound drug was not significantly affected in patients with renal impairment compared with healthy subjects. Hemodialysis conducted 4 or 48 hours after dosing had no significant effect on the pharmacokinetics of aprepitant; less than 0.2% of the dose was recovered in the dialysate.

Hepatic Impairment

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 oral dose of 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_{0-24hr} of aprepitant was 11% lower on Day 1 and 36% lower on Day 3, as compared with healthy subjects given the same regimen. In patients with moderate hepatic impairment (Child-Pugh score 7 to 9), the AUC_{0-24hr} of aprepitant was 10% higher on Day 1 and 18% higher on Day 3, as compared with healthy subjects given the same regimen. These differences in AUC_{0-24hr} are not considered clinically meaningful. There are no clinical or pharmacokinetic data in patients with severe hepatic impairment (Child-Pugh score greater than 9) *[see Use in Specific Populations (8.6)]*.

Body Mass Index (BMI)

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

Drug Interactions Studies

Fosaprepitant, given as a single 150-mg dose, is a weak inhibitor of CYP3A4, with no evidence of inhibition or induction of CYP3A4 observed on Day 4. The weak inhibition of CYP3A4 continues for 2 days after single dose administration of fosaprepitant. Aprepitant is a substrate, an inhibitor, and an inducer of CYP3A4. Aprepitant is also an inducer of CYP2C9.

Fosaprepitant or aprepitant is unlikely to interact with drugs that are substrates for the P-glycoprotein transporter.

Effects of Fosaprepitant/Aprepitant on the Pharmacokinetics of Other Drugs

CYP3A4 Substrates

Midazolam: Fosaprepitant 150 mg administered as a single intravenous dose on Day 1 increased the $AUC_{0-\infty}$ of midazolam by approximately 1.8-fold on Day 1 and had no effect on Day 4 when midazolam was coadministered as a single oral dose of 2 mg on Days 1 and 4 *[see Drug Interactions (7.1)]*.

Corticosteroids:

Reference ID: 4239669

Dexamethasone: Fosaprepitant administered as a single 150 mg 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 *[see Dosage and Administration (2.1), Drug Interactions (7.1)]*.

Methylprednisolone: When oral aprepitant as a 3-day regimen (125-mg/80-mg/80-mg) was administered with intravenous methylprednisolone 125 mg on Day 1 and oral methylprednisolone 40 mg on Days 2 and 3, the AUC of methylprednisolone was increased by 1.34-fold on Day 1 and by 2.5-fold on Day 3 *[see Drug Interactions (7.1)]*.

Chemotherapeutic agents:
Docetaxel: In a pharmacokinetic study, oral aprepitant administered as a 3-day regimen (125-mg/80-mg/80-mg) did not influence the pharmacokinetics of docetaxel.

Vinorelbine: In a pharmacokinetic study, oral aprepitant administered as a 3-day regimen (125-mg/80-mg/80-mg) did not influence the pharmacokinetics of vinorelbine to a clinically significant degree.

Oral contraceptives: When oral aprepitant was administered as a 3-day regimen (125-mg/80-mg/80-mg) with ondansetron and dexamethasone, and coadministered with an oral contraceptive containing ethinyl estradiol and norethindrone, the trough concentrations of both ethinyl estradiol and norethindrone were reduced by as much as 64% for 3 weeks post-treatment *[see Drug Interactions (7.1)]*.

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 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 *[see Drug Interactions (7.1)]*.

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 prior to the administration of the 3-day regimen of oral aprepitant and on Days 4, 8, and 15. This effect was not considered clinically important.

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

5-HT_3 antagonists: In clinical drug interaction studies, aprepitant did not have clinically important effects on the pharmacokinetics of ondansetron, granisetron, or hydrodolasetron (the active metabolite of dolasetron).

<u>Effect of Other Drugs on the Pharmacokinetics of Fosaprepitant/Aprepitant</u>
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 *[see Drug Interactions (7.2)]*.

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 *[see Drug Interactions (7.2)]*.

Diltiazem: In a study in 10 patients with mild to moderate hypertension, administration of 100 mg of fosaprepitant as an intravenous infusion with 120 mg of diltiazem, a moderate CYP3A4 inhibitor

administered three times daily, resulted in a 1.5-fold increase in the aprepitant AUC and a 1.4-fold increase in the diltiazem AUC.

When fosaprepitant was administered with diltiazem, the mean maximum decrease in diastolic blood pressure was significantly greater than that observed with diltiazem alone [24.3 ± 10.2 mm Hg with fosaprepitant versus 15.6 ± 4.1 mm Hg without fosaprepitant]. The mean maximum decrease in systolic blood pressure was also greater after co-administration of diltiazem with fosaprepitant than administration of diltiazem alone [29.5 ± 7.9 mm Hg with fosaprepitant versus 23.8 ± 4.8 mm Hg without fosaprepitant]. Co-administration of fosaprepitant and diltiazem; however, did not result in any additional clinically significant changes in heart rate or PR interval, beyond those changes observed with diltiazem alone *[see Drug Interactions (7.2)]*.

Paroxetine: Coadministration of once daily doses of oral aprepitant 170 mg, with paroxetine 20 mg once daily, resulted in a decrease in AUC by approximately 25% and C_{max} by approximately 20% of both aprepitant and paroxetine. This effect was not considered clinically important.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies were conducted in Sprague-Dawley rats and in CD-1 mice for 2 years. In the rat carcinogenicity studies, animals were treated with oral doses ranging from 0.05 to 1000 mg/kg twice daily. The highest dose produced systemic exposures to aprepitant approximately equivalent to (female rats) or less than (male rats) the human exposure at the RHD of 150 mg. 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 approximately 2 times the human exposure at the RHD of 150 mg. Treatment with aprepitant produced skin fibrosarcomas at 125 and 500 mg/kg/day doses in male mice. Carcinogenicity studies were not conducted with fosaprepitant.

Mutagenesis

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.

Impairment of Fertility

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 RHD of 150 mg and exposure in female rats approximately equivalent to the human exposure).

14 CLINICAL STUDIES

14.1 Prevention of Nausea and Vomiting Associated with HEC

In a randomized, parallel, double-blind, active-controlled study, EMEND for injection 150 mg as a single intravenous infusion (N=1147) was compared to a 3-day oral EMEND regimen (N=1175) in patients receiving a HEC regimen that included cisplatin (≥70 mg/m^2). All patients in both groups received dexamethasone and ondansetron (see Table 7). Patient demographics were similar between the two treatment groups. Of the total 2322 patients, 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 commonly administered were fluorouracil (17%), gemcitabine (16%), paclitaxel (15%), and etoposide (12%).

Table 7
Treatment Regimens in HEC Trial*

	Day 1	Day 2	Day 3	Day 4
EMEND Regimen				
EMEND for injection	150 mg intravenously over 20 to 30 minutes approximately 30 minutes prior to chemotherapy	none	none	none
Oral dexamethasone†	12 mg	8 mg	8 mg twice daily	8 mg twice daily
Ondansetron	Ondansetron‡	none	none	none
Oral EMEND Regimen				
EMEND capsules	125 mg	80 mg	80 mg	none
Oral dexamethasone§	12 mg	8 mg	8 mg	8 mg
Ondansetron	Ondansetron‡	none	none	none

*EMEND for injection placebo, EMEND capsules placebo and dexamethasone placebo (in the evenings on Days 3 and 4) were used to maintain blinding.

†Dexamethasone was administered 30 minutes prior to chemotherapy treatment on Day 1 and in the morning on Days 2 through 4. Dexamethasone was also administered in the evenings on Days 3 and 4. The 12 mg dose of dexamethasone on Day 1 and the 8 mg once daily dose on Day 2 reflects a dosage adjustment to account for a drug interaction with the EMEND for injection regimen *[see Clinical Pharmacology (12.3)].*

‡Ondansetron 32 mg intravenous was used in the clinical trials of EMEND. Although this dose was used in clinical trials, this is no longer the currently recommended dose. Refer to the ondansetron prescribing information for the current recommended dose.

§Dexamethasone was administered 30 minutes prior to chemotherapy treatment on Day 1 and in the morning on Days 2 through 4. The 12 mg dose of dexamethasone on Day 1 and the 8 mg once daily dose on Days 2 through 4 reflects a dosage adjustment to account for a drug interaction with the oral EMEND regimen *[see Clinical Pharmacology (12.3)].*

The efficacy of EMEND for injection was evaluated based on the primary and secondary endpoints listed in Table 8 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%.

Reference ID: 4239669

Table 8
Percent of Patients Receiving Highly Emetogenic Chemotherapy Responding by Treatment Group and Phase — Cycle 1

ENDPOINTS	EMEND for Injection Regimen (N = 1106)* %	Oral EMEND 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 Prevention of Nausea and Vomiting Associated with MEC

In a randomized, parallel, double-blind, active comparator-controlled study, EMEND for injection 150 mg as a single intravenous infusion (N=502) in combination with ondansetron and dexamethasone (EMEND regimen) was compared with ondansetron and dexamethasone alone (standard therapy) (N=498) (see Table 9) in patients receiving a MEC regimen. Patient demographics were similar between the two treatment groups. Of the total 1,000 patients included in the efficacy analysis, 41% were men, 84% White, 4% Asian, 1% American Indian/Alaska Native, 2% Black, 10% Multi-Racial, and 19% Hispanic/Latino ethnicity. Patient ages ranged from 23 to 88 years of age, with a mean age of 60 years. The most commonly administered MEC chemotherapeutic agents were carboplatin (51%), oxaliplatin (24%), and cyclophosphamide (12%).

Table 9
Treatment Regimens in MEC Trial*

	Day 1	Day 2	Day 3
EMEND Regimen			
EMEND for Injection	150 mg intravenously over 20 to 30 minutes approximately 30 minutes prior to chemotherapy	none	none
Oral Dexamethasone†	12 mg	none	none
Oral Ondansetron‡	8 mg for 2 doses	none	none
Standard Therapy			
Oral Dexamethasone	20 mg	none	none
Oral Ondansetron‡	8 mg for 2 doses	8 mg twice daily	8 mg twice daily

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

The primary endpoint was complete response (defined as no vomiting and no rescue therapy) in the delayed phase (25 to 120 hours) of chemotherapy-induced nausea and vomiting. The results by treatment group are shown in Table 10.

Table 10
Percent of Patients Receiving Moderately Emetogenic Chemotherapy Responding by Treatment Group

ENDPOINTS	EMEND for Injection Regimen (N = 502)* %	Standard Therapy Regimen (N = 498)* %	P-Value	Treatment Difference (95% CI)
PRIMARY ENDPOINT				
Complete Response†				
Delayed phase‡	78.9	68.5	<0.001	10.4 (5.1, 15.9)

*N: Number of patients included in the intention to treat population.
†Complete Response = no vomiting and no use of rescue therapy.
‡Delayed phase = 25 to 120 hours post-initiation of chemotherapy.

16 HOW SUPPLIED/STORAGE AND HANDLING

No. 3941 — Single-dose glass vial containing 150 mg of fosaprepitant as a white to off-white lyophilized powder for reconstitution. Supplied as follows:

NDC 0006-3941-32 1 vial per carton.

Storage

Emend for injection vials must be refrigerated, store at 2°C-8°C (36°F-46°F).

The reconstituted final drug solution is stable for 24 hours at ambient room temperature [at or below 25°C (77°F)].

17 PATIENT COUNSELING INFORMATION

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

Hypersensitivity

Advise patients that hypersensitivity reactions, including anaphylaxis and anaphylactic shock, have been reported in patients taking EMEND. Advise patients to seek immediate medical attention if they experience signs or symptoms of a hypersensitivity reaction, such as hives, rash and itching, skin peeling or sores, flushing, difficulty in breathing or swallowing, or dizziness, rapid or weak heartbeat or feeling faint *[see Warnings and Precautions (5.2)]*.

Infusion Site Reactions

Advise patients to seek medical attention if they experience new or worsening signs or symptoms of an infusion site reaction, such as erythema, edema, pain, necrosis, vasculitis, or thrombophlebitis at or near the infusion site *[see Warnings and Precautions (5.3)]*.

Drug Interactions

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

Warfarin: Instruct patients on chronic warfarin therapy to follow instructions from their healthcare provider regarding blood draws to monitor their INR during the 2-week period, particularly at 7 to 10 days, following initiation of EMEND with each chemotherapy cycle *[see Warnings and Precautions (5.4)]*.

Hormonal Contraceptives: Advise patients that administration of EMEND may reduce the efficacy of hormonal contraceptives. Instruct patients to use effective alternative or back-up methods of contraception (such as condoms and spermicides) during treatment with EMEND and for 1 month following administration of EMEND *[see Warnings and Precautions (5.5), Use in Specific Populations (8.3)]*.

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

Manufactured by:
Patheon Manufacturing Services LLC, 5900 Martin Luther King Jr. Highway, Greenville, NC 27834, USA

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

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uspi-mk0517-iv-edta18-1803r016

Patient Information
EMEND® (EE mend)
(fosaprepitant)
for Injection

Read this Patient Information before you start receiving EMEND for Injection and each time you are scheduled to receive EMEND for Injection. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or treatment.

What is EMEND for Injection?

EMEND for Injection is a prescription medicine used with other medicines that treat nausea and vomiting in adults to prevent nausea and vomiting caused by certain anti-cancer (chemotherapy) medicines.

- EMEND for Injection is not used to treat nausea and vomiting that you already have.
- It is not known if EMEND for Injection is safe and effective in children.

Who should not receive EMEND for Injection?

Do not receive EMEND for Injection if you:

- are allergic to fosaprepitant, aprepitant, or any of the ingredients in EMEND for Injection. See the end of this leaflet for a complete list of the ingredients in EMEND for Injection.
- are taking pimozide (ORAP®)

What should I tell my healthcare provider before receiving EMEND for Injection?

Before receiving EMEND for Injection, tell your healthcare provider if you:

- have liver problems
- are pregnant or plan to become pregnant. It is not known if EMEND for Injection can harm your unborn baby.
    - Women who use birth control medicines containing hormones to prevent pregnancy (birth control pills, skin patches, implants, and certain IUDs) should also use a backup method of birth control that does not contain hormones, such as condoms and spermicides, during treatment with EMEND for Injection and for 1 month after receiving EMEND for Injection.
- are breastfeeding or plan to breastfeed. It is not known if EMEND for Injection passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby if you receive EMEND for Injection.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

EMEND for Injection may affect the way other medicines work, and other medicines may affect the way EMEND for Injection works, causing serious side effects.

Know the medicines you take. Keep a list of them to show your healthcare provider or pharmacist when you get a new medicine.

How will I receive EMEND for Injection?

EMEND for Injection is given on Day 1. It will be given to you by intravenous (IV) infusion in your vein about 30 minutes before you start your chemotherapy treatment.

- If you take the blood thinner medicine warfarin sodium (COUMADIN®, JANTOVEN®), your healthcare provider may do blood tests after you receive EMEND for Injection to check your blood clotting.

What are the possible side effects of EMEND for Injection?

EMEND for Injection may cause serious side effects, including:

- **Serious allergic reactions.** Allergic reactions can happen with EMEND for Injection and may be serious. Tell your doctor or nurse right away if you have hives, rash, itching, flushing or redness of

your face or skin, trouble breathing or swallowing, dizziness, a rapid or weak heartbeat, or you feel faint during or soon after you receive EMEND for Injection, as you may need emergency medical care.

- Severe skin reactions, which may include rash, skin peeling, or sores, may occur.
- Infusion site reactions (ISR) at or near the infusion site have happened with EMEND for Injection.

  Most severe ISR have happened with a certain type of chemotherapy medicine that can burn or blister your skin (vesicant) with side effects, including pain, swelling and redness. Death of skin tissue (necrosis) has happened in some people getting this type of chemotherapy medicine. Most ISR can happen with the first, second, or third dose and some can last up to 2 weeks or longer. Tell your healthcare provider right away if you get any infusion site side effects.

The most common side effects of EMEND for Injection include:

- tiredness
- diarrhea
- low white blood cell and red blood cell counts
- weakness
- feeling weak or numb in your arms and legs
- painful, difficult, or changes in your digestion (dyspepsia)
- urinary tract infection
- pain in your arms and legs

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all of the possible side effects of EMEND for Injection. For more information ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of EMEND for Injection

If you would like more information about EMEND for Injection, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about EMEND for Injection that is written for health professionals. For more information about EMEND for Injection call 1-800-622-4477 or go to www.emend.com.

What are the ingredients in EMEND for Injection?

Active ingredient: fosaprepitant

Inactive ingredients: edetate disodium, polysorbate 80, lactose anhydrous, sodium hydroxide and/or hydrochloric acid (for pH adjustment)

Manufactured for: Merck Sharp & Dohme Corp., a subsidiary of **MERCK & CO., INC.,** Whitehouse Station, NJ 08889, USA
Manufactured by: Patheon Manufacturing Services LLC, 5900 Martin Luther King Jr. Highway, Greenville, NC 27834, USA
For patent information: www.merck.com/product/patent/home.html
The brands listed in the above sections “Who should not receive EMEND for Injection?” and “How will I receive EMEND for Injection?” are the registered trademarks of their respective owners and are not trademarks of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
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usppi-mk0517-iv-1803r013

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: March 2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022023Orig1s018

MEDICAL REVIEW(S)

Clinical Memorandum
Prior Approval Labeling Supplement and Change in Status of Trackable Safety Issue
Division of Gastroenterology & Inborn Errors Products (DGIEP)

NDA: 022023/S-018
Safety Issue Name: Fosaprepitant Injection and Infusion Site Reactions
Safety Application Number: 1845
Sponsor: Merck
Product: EMEND (fosaprepitant) for Injection
Drug Class: Substance P/NK1 Receptor Antagonist
Safety Reviewer: Sandhya Apparaju, Ph.D.
Team Leader: Preeti Venkataraman, MD
Deputy Director for Safety: Joyce Korvick, MD
Safety RPM: Jacqueline Lee, PharmD

Current Status of TSI	**Active** ☒	**Ongoing** ☐	**Closed** ☐	**Cancelled** ☐
Desired/New Status of TSI	**Active** ☐	**Ongoing** ☐	**Closed** ☒	**Cancelled** ☐

1. Background of the Safety Issue

EMEND (fosaprepitant) for Injection was originally approved on January 1, 2008 for the prevention of chemotherapy induced nausea and vomiting (CINV) in adults. Fosaprepitant is a phosphorylated prodrug that is rapidly converted to aprepitant after IV administration. Infusion site reactions (ISRs) were noted in the clinical development program of EMEND for Injection and are currently included in the approved labeling under Adverse Reactions- Section 6.1 Clinical Trials Experience.

In June, 2017 the Division of Pharmacovigilance I (DPV-I) completed an analysis of the post-marketing adverse event reports of ISRs associated with the use of fosaprepitant for injection. Reviewers utilized the information contained in the FDA Adverse Event Reporting System (FAERS) database and medical literature (retrospective studies) in their review. In this regard, please refer to Pharmacovigilance review by Dr. Kimberley Swank, dated 06/16/2017 in DARRTs under Safety –TSI 1845.

Key findings from the DPV-I review are briefly presented below:

- 73 unique cases of ISRs were identified in the FAERS database search [August 1, 2010 to February 3, 2017], of which 41 resulted in a serious outcome including one hospitalization and eight disability cases. 20 of 73 reports were from Japan, where a more concentrated form of fosaprepitant is infused compared (1.5 mg/mL vs. 1 mg/mL in the U.S.).
- Majority of ISRs (39 of 73) occurred with the first (n=21), second (n=10), or third (n=8) *[single intravenous]* dose of fosaprepitant.

Reference ID: 4240153

- Reactions that were deemed to be mild to moderate in severity included pain, erythema, swelling, and phlebitis which discontinued shortly after drug discontinuation or with additional treatment.
- The remaining 34 cases reported one or more ISRs that were severe (n=28), resulted in prolonged sequelae of at least two weeks duration (n=12), and limited activities of daily living (ADLs) (n=6).
- The severe ISRs included extravasation reaction (n =18), 'constricted or hardened veins' (n =5), necrosis (n =3), thrombosis (n =3), needing surgical intervention (n =3), and vasculitis (n =2).
- Information on the administration site (peripheral vs. central) was unknown in 59 of 73 cases (14 received peripheral administrations); concomitant use of vesicant chemotherapy (anthracyclines) was unavailable in 32 of 73 cases.
- In 29 cases, concomitant anthracycline-based chemotherapy was reported; DPV reviewers also note that the ISR occurred temporal to administration of fosaprepitant, but may have worsened or recurred after chemotherapy administration.
- Of the 29 patients that received vesicant chemotherapy, 19 reported a severe ISR.
- Reviewers also note that the low incidence rate and lack of severe ISRs identified in the clinical trials of EMEND for Injection may have been due to the short duration of the trials (i.e., single dose therapy) and use of concomitant non-anthracycline (i.e., non-vesicant) chemotherapy regimens.

DPV-I recommended the following for consideration:

1. Addition of ISRs, particularly in patients receiving concomitant anthracycline-based chemotherapy regimens, to the Warnings and Precautions section.
2. Adding mitigating strategies to the label

2. Regulatory Actions

A Tracked Safety Issue (TSI) was opened on 10/11/2017 (# 1845) for EMEND for Injection and Infusion Site Reactions. The FDA considers this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA. This reviewer agrees with DPV-I's recommendations, and DGIEP worked collaboratively with DPV-I to propose ISR-related revisions to the Prescribing Information of EMEND for Injection. Relevant edits to the Patient Package Insert (PPI) were also proposed by the Division of Medical Policy Programs (DMPP). A Section 901 Safety Labeling Change (SLC) Notification was issued by FDA to the Sponsor on 01/23/2018 including specific labeling changes to Highlights, Warnings and Precautions, Patient Counseling Information and to the PPI. In response to the SLC letter, the Sponsor submitted a Prior-Approval Labeling Supplement on 02/22/2018 (NDA 22023/S-018) with proposed edits. After internal review and discussion, the final labeling language was agreed upon with the Sponsor on 03/23/2018. The following is a summary of the current wording and final agreed-upon labeling language for EMEND for Injection:

Reference ID: 4240153

	Current Label (08/09/2017 version)	**Final Agreed-upon Wording (03/2018)**
Highlights	*N/A*	Infusion Site Reactions (including thrombophlebitis, necrosis, and vasculitis): Majority of reactions reported in patients receiving vesicant chemotherapy. Avoid infusion into small veins. Discontinue infusion and administer treatment if a severe reaction develops. (5.3)
Warnings and Precautions	*N/A*	5.3 Infusion Site Reactions Infusion site reactions (ISRs) have been reported with the use of EMEND for injection *[see Adverse Reactions (6.1)]*. The majority of severe ISRs, including thrombophlebitis and vasculitis, were reported with concomitant vesicant (anthracycline-based) chemotherapy administration, particularly when associated with extravasation. Necrosis was also reported in some patients with concomitant vesicant chemotherapy. Most ISRs occurred with the first, second or third exposure to single doses of EMEND for injection and in some cases, reactions persisted for two weeks or longer. Treatment of severe ISRs consisted of medical, and in some cases surgical, intervention. Avoid infusion of EMEND for injection into small veins or through a butterfly catheter. If a severe ISR develops during infusion, discontinue the infusion and administer appropriate medical treatment.
Patient Counseling Information (17)	*Hypersensitivity and Infusion Site Reactions* *[Excerpt] Advise patients local infusion site reactions, such as erythema, edema, pain, or thrombophlebitis, can also occur and instruct them on how to care for the local reaction and when to seek further evaluation.*	Infusion Site Reactions Advise patients to seek medical attention if they experience new or worsening signs or symptoms of an infusion site reaction, such as erythema, edema, pain, necrosis, vasculitis, or thrombophlebitis at or near the infusion site *[see Warnings and Precautions (5.3)]*.

Reference ID: 4240153

Patient Package Insert:	*Infusion-site side effects with EMEND for Injection may include pain, hardening, redness or itching at the site of infusion. Swelling (inflammation) of a vein caused by a blood clot can also happen at the infusion site. Tell your healthcare provider if you get any infusion-site side effects.*	Infusion site reactions (ISR) at or near the infusion site have happened with EMEND for Injection. Most severe ISRs have happened with a certain type of chemotherapy medicine that can burn or blister your skin (vesicant) with side effects, including pain, swelling and redness. Death of skin tissue (necrosis) has happened in some people getting this type of chemotherapy medicine. Most ISR can happen with the first, second, or third dose and some can last up to 2 weeks or longer. Tell your healthcare provider right away if you get any infusion site side effects.

3. Basis for Decision of Application Status Change

An approval letter for NDA 22023/S-018 was issued on 03/26/2018. In this regard, also refer to the final approved product label for EMEND for Injection attached to the letter. Necessary safety reviews and regulatory actions are complete addressing the intent of this TSI.

TSI #1845 is considered closed.

Reference ID: 4240153

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SANDHYA K APPARAJU
03/27/2018

PREETI VENKATARAMAN
03/27/2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022023Orig1s018

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR PATIENT LABELING REVIEW CONSULTATION

TO:

CDER-DMPP-PatientLabelingTeam

FROM: (Name/Title, Office/Division/Phone number of requestor)
Jacqueline LeeHoffman/SRPM, OND/ODEIII/DGIEP
240-402-8689

REQUEST DATE:
11/28/17

NDA/BLA NO.:
22023

TYPE OF DOCUMENTS: PI/MG consult for SLC
(PLEASE CHECK OFF BELOW)
Revise the PPI based on proposed revisions to injection site reaction (ISR) to the PI for SLC

NAME OF DRUG:
Emend (fosaprepitant IV)

PRIORITY CONSIDERATION:
Standard

CLASSIFICATION OF DRUG:
Antiemetic/Substance P/Neurokinin 1 receptor antagonist

DESIRED COMPLETION DATE
(Generally 2 Weeks after receiving substantially complete labeling)
2 weeks

SPONSOR:
Merck Sharp and Dohme Corp

PDUFA Date:

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
☒ PATIENT PACKAGE INSERT (PPI)
☐ MEDICATION GUIDE
☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
☐ ORIGINAL NDA/BLA/ANDA
☐ EFFICACY SUPPLEMENT
☐ SAFETY SUPPLEMENT
☐ LABELING SUPPLEMENT
☐ MANUFACTURING (CMC) SUPPLEMENT
☐ PLR CONVERSION

REASON FOR LABELING CONSULT
☐ INITIAL PROPOSED LABELING
☐ LABELING REVISION

EDR link to submission:

Please Note: DMPP uses substantially complete labeling, which has already been marked up by the CDER Review Team, when reviewing MedGuides, IFUs, and PPIs. Once the substantially complete labeling is received, DMPP will complete its review within 14 calendar days. Please provide a copy of the sponsor's proposed patient labeling in Word format.

COMMENTS/SPECIAL INSTRUCTIONS:

DGIEP submits consult to revise the PPI based on our proposed revisions (ISRs) to the PI. Please see the attached sharepoint for the track changes to the PI.

Emend IV ISR safety labeling

SIGNATURE OF REQUESTER
Jackie LeeHoffman11-28-17

SIGNATURE OF RECEIVER	

Version: 06/06/2016

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/s/

JACQUELINE D LEEHOFFMAN
03/09/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR PATIENT LABELING REVIEW CONSULTATION

TO:

CDER-DMPP-PatientLabelingTeam

FROM: (Name/Title, Office/Division/Phone number of requestor)
Jacqueline LeeHoffman/SRPM, OND/ODEIII/DGIEP
240-402-8689

REQUEST DATE:
11/28/17

NDA/BLA NO.:
22023

TYPE OF DOCUMENTS: PI/MG consult for SLC
(PLEASE CHECK OFF BELOW)
Revise the PPI based on proposed revisions to injection site reaction (ISR) to the PI for SLC

NAME OF DRUG:
Emend (fosaprepitant IV)

PRIORITY CONSIDERATION:
Standard

CLASSIFICATION OF DRUG:
Antiemetic/Substance P/Neurokinin 1 receptor antagonist

DESIRED COMPLETION DATE
(Generally 2 Weeks after receiving substantially complete labeling)
2 weeks

SPONSOR:
Merck Sharp and Dohme Corp

PDUFA Date:

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
☒ PATIENT PACKAGE INSERT (PPI)
☐ MEDICATION GUIDE
☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
☐ ORIGINAL NDA/BLA/ANDA
☐ EFFICACY SUPPLEMENT
☐ SAFETY SUPPLEMENT
☐ LABELING SUPPLEMENT
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