CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 022023/S-014

Trade Name: **EMEND**

Generic Name: **fosaprepitant dimeglumine**

Sponsor: **Merck Sharp & Dohme Corp.**

Approval Date: December 2, 2016

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 and (2) delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC).

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APPLICATION NUMBER:

NDA 022023/S-014

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022023/S-014

APPROVAL LETTER

Merck Sharp & Dohme Corp.
A subsidiary of Merck & Co., Inc.
Attention: Nicholas W. Andrew, Director, Regulatory Affairs
1 Merck Drive, P.O. Box 100
Whitehouse Station, NJ 08889

Dear Mr. Andrew:

Please refer to your Supplemental New Drug Application (sNDA) dated and received August 4, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Emend®(fosaprepitant dimeglumine) for injection, 150 mg/mL.

We also refer to our approval letter dated December 2, 2016, which inadvertently omitted the specified decreased dose of the inactive ingredient, ETDA contained in the drug product and the approved labeling. This replacement approval letter incorporates the correction of the error. The effective approval date will remain December 2, 2016, the date of the original approval letter.

This Prior Approval supplemental new drug application provides for a re-formulated drug product containing 5.4 mg of EDTA per dose.

We have completed our review of this supplemental new drug application. This supplement is **approved**.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this corrected 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 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 of this corrected letter, amend all pending supplemental applications that includes 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).

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the enclosed carton and immediate container labels, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008).* Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 022023/S-014**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Grecia C. Edwards, Regulatory Business Process Manager, at (240) 402-1773.

Sincerely,

{See appended electronic signature page}

David B. Lewis, Ph.D.
Division of Postmarketing Activities I
Branch II Chief (acting)
Office of Lifecycle Drug Products (OLDP)
Office of Pharmaceutical Quality

David
Lewis

Digitally signed by David Lewis
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 022023/S-014

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 dimeglumine) for injection, for intravenous use
Initial U.S. Approval: 2008

----------RECENT MAJOR CHANGES----------
Dosage and Administration (2.1, 2.2) 02/2016

----------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, lyophilized powder in single-dose vial for reconstitution (3)

----------CONTRAINDICATIONS----------
- Known hypersensitivity to any component of this drug. (4)
- 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: These may occur during infusion; if symptoms occur, discontinue the drug. Do not reinitiate the infusion if symptoms occur with first-time use. (5.2)
- Warfarin (a CYP2C9 substrate): Risk of decreased INR of prothrombin time; monitor INR in 2–week period, particularly at 7 to 10 days, following initiation of EMEND. (5.3, 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. (5.4, 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, 5.2, 5.3, 5.4, 7.1, 7.2)

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

Revised: XX/20XX

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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 prescr bing 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)]*.

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, 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 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

Hypersensitivity reactions during infusion of fosaprepitant including flushing, erythema, dyspnea, and anaphylaxis have been reported. If symptoms occur, discontinue the infusion and administer appropriate medical therapy. Do not reinitiate the infusion in patients who experience these symptoms during first-time use.

5.3 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)]*.

5.4 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.

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

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.

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

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

7 DRUG INTERACTIONS

7.1 Effect of 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 (5.4), 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 (5.3), 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.

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) and 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.

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.

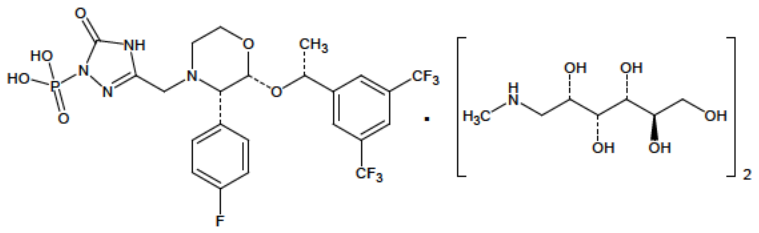
In the event of overdose, EMEND should be discontinued and general supportive treatment and monitoring should be provided. Because of the antiemetic activity of EMEND, drug-induced emesis may not be effective in cases of EMEND overdosage.

Aprepitant is not removed by hemodialysis.

11 DESCRIPTION

EMEND (fosaprepitant dimeglumine) for injection is a sterile, lyophilized 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 245.3 mg of fosaprepitant dimeglumine equivalent to 150 mg of fosaprepitant free acid 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). Fosaprepitant dimeglumine hereafter will be referred to as fosaprepitant.

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 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 $5\text{-}HT_3$-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 14% and 22% higher in females as compared with males. The half-life of aprepitant is 25% lower in females as compared with males and T_{max} occurs at approximately the same time. These differences are not considered clinically meaningful.

Race/Ethnicity

Following oral administration of a single dose of aprepitant, ranging from 40 mg to 375 mg, the $AUC_{0\text{-}24hr}$ and C_{max} are approximately 42% and 29% higher in Hispanics as compared with Caucasians. The $AUC_{0\text{-}24hr}$ and C_{max} were 62% and 41% higher in Asians as compared to Caucasians. There was no difference in $AUC_{0\text{-}24hr}$ or C_{max} between Caucasians and Blacks. These differences are not considered clinically meaningful.

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 $AUC_{0\text{-}\infty}$ 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 $AUC_{0\text{-}\infty}$ of total aprepitant decreased by 42% and C_{max} decreased by 32%. Due to modest decreases in protein binding of aprepitant in patients with renal disease, the AUC of pharmacologically active unbound drug was not significantly affected in patients with renal impairment compared with healthy subjects. Hemodialysis conducted 4 or 48 hours after dosing had no significant effect on the pharmacokinetics of aprepitant; less than 0.2% of the dose was recovered in the dialysate.

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 $AUC_{0\text{-}24hr}$ of aprepitant was 11% lower on Day 1 and 36% lower on Day 3, as compared with healthy subjects given the same regimen. In patients with moderate hepatic impairment (Child-Pugh score 7 to 9), the $AUC_{0\text{-}24hr}$ of aprepitant was 10% higher on Day 1 and 18% higher on Day 3, as compared with healthy subjects given the same regimen. These differences in $AUC_{0\text{-}24hr}$ are not considered clinically meaningful. 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, $AUC_{0\text{-}24hr}$ and C_{max} of aprepitant decrease by 11%. BMI of subjects in the analysis ranged from 18 kg/m^2 to 36 kg/m^2. This change is not considered clinically meaningful.

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 $AUC_{0\text{-}\infty}$ 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.

Corticosteroids:

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).

Effect of Other Drugs on the Pharmacokinetics of Fosaprepitant/Aprepitant

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 $\pm$ 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%.

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. 3061 — One 150-mg White to off-white lyophilized powder in single-dose glass vial, 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 and Infusion Site Reactions

Advise patients that hypersensitivity reactions, including anaphylaxis, have been reported in patients taking EMEND. Advise patients to stop taking EMEND and seek immediate medical attention if they experience signs or symptoms of a hypersensitivity reaction, such as hives, rash and itching, skin peeling or sores, or difficulty in breathing or swallowing. Advise patients who develop an infusion site reaction such as erythema, edema, pain, or thrombophlebitis on how to care for the local reaction and when to seek further evaluation.

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 (5.3)]*.

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 (5.4), 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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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 022023/S-014

CHEMISTRY REVIEW(S)

Office of Lifecycle Drug Products
Division of Post-Marketing Activities I
Review of Chemistry, Manufacturing, and Controls

1. **NDA Supplement Number: NDA 22-023/S-014**

2. **Submission(s) Being Reviewed**:

Submission	Type	Submission Date	CDER Stamp Date	Assigned Date	PDUFA Goal Date	Review Date
Supplement	PA	8/4/16	8/4/16	8/4/16	12/4/17	11/29/16

3. **Proposed Changes**: Re-formulated drug product containing a reduced quantity of EDTA.

4. **Review #**: 1

5. **Clinical Review Division**: DGIEP

6. **Name and Address of Applicant**:
Merck Sharp & Dohme Corp., A subsidiary of Merck & Co., Inc.
1 Merck Drive
P.O.Box 100, Whitehouse Station, NJ, 08889-0100

7. **Name of the Drug Product:**

Drug Name	Dosage Form	Strength	Route of Administration	Rx or OTC	Special Product
Emend®(fosaprepitant dimeglumine) for injection	Lyophilized powder	150 mg/ml	Intravenous	Rx	N/A

8. Chemical Name and Structure of Drug Substance:

9. Indication:
Prevention for acute and delayed nausea and vomiting with moderate to high emetogenic chemotherapy

10. Supporting/Relating Documents: None

11. Consults:

Consults	Recommendation	Date	Reviewer
OPF/Facility	N/A		
OLDP Lifecycle API	N/A		
Microbiology	N/A		
Pharm/Tox	N/A		
Biopharm	N/A		
Statistics	N/A		
DMEPA	N/A		
CDRH/ODE	N/A		
CDRH/OC	N/A		
EA	N/A		

12. Executive Summary:

This application contains information including rationale and background for the development of a reduced EDTA formulation for Fosaprepitant Dimeglumine for Injection 150mg. To reflect the reduced EDTA formulation, updated Common Technical Document (CTD) sections are provided for pharmaceutical development, composition, stability and manufacturing process. (b) (4)

The reduced-EDTA formulation is identical to the current formulation with the exception of a reduced quantity of EDTA (from 18.8 mg/dose to 5.4 mg/dose). All other ingredients are utilized in the same proportion. This re-formulation only concerns the 150-mg product. (b) (4) The submitted stability data supports the current 24 month expiry dating. The applicant provided representative labels and labeling for the re-formulated product, containing information corresponding tothe reduced-EDTA formulation. The re-formulated product was assigned a new NDC number.

13. Conclusions & Recommendations:

From CMC's standpoint, this supplement **is recommended** for approval.

14. Comments/Deficiencies to be conveyed to Applicant: None

15. Primary Reviewer:
Hossein Khorshidi, CMC reviewer, Branch II, Division of Post-Marketing Activities I, Office of Lifecycle Drug Products, Office of Pharmaceutical Quality (OPQ)

16. Secondary Reviewer:
David Lewis, Branch Chief, Branch II, Division of Post-Marketing Activities I, Office of Lifecycle Drug Products, OPQ

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David Lewis

Digitally signed by David Lewis
Date: 12/01/2016 01:29 57PM
GUID: 508da72000029f287fa31e664741b577
Comments: concur; recommend approval from the standpoint of CMC.

Hossein Khorshidi

Digitally signed by Hossein Khorshidi
Date: 12/01/2016 12:44 33PM
GUID: 508da72000029f4c67cf1b39a1d92654

Initial Quality Assessment - OLDP Division of Post-Marketing Activities I

NDA: 22-023	**NME:** Yes ☐ No ☒	**Original NDA Approval Date:**
Supplement: S-014	**Applicant:** Merck	**Product:** Emend™ (fosaprepitant dimeglumine) for injection
Clinical Division: DGIEP		
Managed by: OND ☐ *Efficacy* ☐ *Labeling* ☐		**OPQ** ☒
Receipt Date: 8/04/2016		**PDUFA Goal Date: 12/04/2016**
Proposed changes: re-formulated drug product containing a reduced quantity of EDTA		
Submitted as: Paper ☐ Electronic ☒	**Complete Response:** Yes ☐ No ☒ **Previous Reviewer:**	
Submitted Category: CBE-0 ☐ CBE-30 ☐ PA ☒		**Final Category:** CBE-0 ☐ CBE-30 ☐ PA ☒
Expedited Review Requested: Yes ☐ No ☒	**Drug Shortage:** Yes ☐ No ☒	**Bundled Supplements:** Yes ☐ No ☒

Facility Entry/Consults Needed:

Facility Entry: ☒ Micro: ☐ Biopharm: ☐ Pharm/tox: ☐

Statistics: ☐ CDRH: ☐ OPF: ☐ DMEPA: ☐

Other:

DMF Review: ☐

Comments: the NDA 22-023 drug product, Emend™ contains fosaprepitant dimeglumine (a pro-drug of aprepitant) in an injectable formulation. The Emend™ injection product was formulated to contain edetate disodium (EDTA) (b) (4)

The original Emend™ formulation contained 18.8 mg EDTA per 150-mg dose (vial). (b) (4)

(b) (4)

Per FDA-applicant agreement,

(b) (4)

(b) (4) In relation to the data submission requirements to support a change to the current approved formulation (reduction of EDTA quantity from 18.8mg/dose to 5.4 mg/dose), FDA agreed that clinical data would not be required and submission of the following information to support the change appeared reasonable.

- Description and Composition
- Formulation Development (development work/data to support reformulation)
- Batch Formula
- Description of Manufacturing Process and Process Controls
- Comparative Batch Analysis
- Three months Stability Data on 3 batches (accelerated and refrigerated) with commitment to provide long-term refrigerated, and reconstituted stability data.

FDA further requested that this formulation change be submitted as a Prior Approval supplement (PAS).

The reduced-EDTA formulation is identical to the current formulation with the exception of a reduced quantity of EDTA (from 18.8 mg/dose to 5.4 mg/dose). All other ingredients are utilized in the same proportion. This re-formulation only concerns the 150-mg product.

The applicant provided exhibit stability data (full-scale batches, proposed manufacturing site, through 24 months long-term [5°C] and through 6 months, accelerated [25°C and 60% RH]). In addition, supportive stability data is provided, through 36 months (alternate site, smaller-scale).

(b) (4)

The re-formulated product will be manufactured and tested at the following facilities:

(b) (4)

According to the 356H, these facilities are not new to the application, but according to the cover letter, there has been a change to the analytical testing sites. The OPRO RBPM should verify which sites are new to the application and have them added to Panorama Inspection View.

Proposed labeling is provided for the re-formulated product; this should be consulted to OSE-DMEPA.

(b) (4)

PAS is the correct submission strategy. This supplement is to be managed by OLDP (per OND project manager, Mary Chung, per request from OLDP).

QAL: David Lewis	**Date:** 8/16/2016
Assigned Reviewer: Hossein (Shawn) Khorshidi	**RBPM:** Grecia Edwards

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 022023/S-014

OTHER REVIEW(S)

REGULATORY PROJECT MANAGER LABELING REVIEW
Review #1

Office of New Drug Quality Assessment

Application Number: NDA 022023/S-014

Name of Drug: EMEND® (Fosaprepitant Dimeglumine) for Injection

Applicant: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.

Material Reviewed:

Material	Submit Date	Receipt Date	Compared to
Package Insert	8/4/2016	8/4/2016	Last approved in 2/1/2016 in S-006
Carton and Container Labels	8/4/2016	8/4/2016	Compared to the approved labeling in S-006 submission on 2/1/2016

Background and Summary

NDA 022023, EMEND™ (fosaprepitant dimeglumine) for Injection was approved on January 25, 2008, as an antiemetic agent in combination with other antiemetic agents, for the prevention of:

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

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

[redacted] (b) (4)

NDA 022023/S-014 was submitted on August 4, 2016, as a PAS, provides for re-formulated drug product containing a reduced quantity of product containing 5.4 mg of EDTA per dose.

CMC recommends approval. (see review dated, November 29, 2016)

Review

This comparison was done by visually comparing the proposed to the last submitted or approved labeling on file.

The following are the assessments for each change identified:

Package Insert:

1. Modification of product description to reflect new dosage of inactive ingredient, EDTA to 5.4 mg (identified on page 8):

Comment: This editorial change is acceptable

2. Modification of the "How SUPPLIED/STORAGE AND HANDLING" section to reflect updated NDC # (page 15):

(b) (4)

Comment: This editorial change is acceptable.

3. **Modification to the Manufactured by section (page 16):**

(b) (4)

Comment: This editorial change is acceptable.

Minor Editorial and Acceptable Changes (pages 1 and 5):

Comment: These minor editoral changes are acceptable.

Carton Label:

1. The inactive ingredients' section, on the container carton, has been revised to reflect the lower amount of edetate disodium, 5.4 mg, used in proposed formulation.

2. A new NDA number (NDC # 0006-3941-32) has been assigned for both the container label and carton to differentiate between 18.8 mg vs new 5.4 mg dose of ETDA.

3. The copyright year has been updated on the container carton.

4. Modification of the Merck component number on container label and carton.

5. Artwork modification to prepare for serialization in accordance to requirements starting on or before November 27, 2017.

Comment: These expected changes are associated with the new dosage of inactive ingredient, provided for in this supplement and conform to applicable regulations. Acceptable (see below attachments).

Recommendations

The changes to the package insert and carton label are acceptable. The supplement is recommended for approval.

Grecia C. Edwards, PharmD.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality Date

Okubadejo (Gbenga) Olugbenga , PharmD.
Quality Assessment Lead (Acting) Date
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality

2 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

Olugbenga (Gbenga) Okubadejo

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Grecia Edwards

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Date: 2/13/2017 09:56:51PM
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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	October 31, 2016
Requesting Office or Division:	Division of Gastroenterology and Inborn Error Products (DGIEP)
Application Type and Number:	NDA 22023/S-14
Product Name and Strength:	Emend (fosaprepitant dimeglumine) for Injection 150 mg
Product Type:	Single ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Merck & Co. Inc.
Submission Date:	August 4, 2016
OSE RCM #:	2016-1954
DMEPA Primary Reviewer:	Sherly Abraham, RPh
DMEPA Team Leader:	Mishale Mistry, PharmD, MPH

1 REASON FOR REVIEW

This review evaluates the labels and labeling for Emend for Injection (NDA 22023/S-014), submitted on August 4, 2016 as a Prior Approval Supplement (PAS). (b) (4) The PAS also proposes to change the National Drug Code (NDC) number to reflect the newer product with lower EDTA. The Division of Gastroenterology and Inborn Error Products (DGIEP) requested that DMEPA review the proposed prescribing information, carton labeling, and container labels for any areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Merck and Co submitted a Prior Approval Supplement which proposes to change the National Drug Code (NDC) number in the prescribing information, carton label and container labeling to reflect the newer product with lower EDTA. (b) (4) , the sponsor is submitting this supplement to reduce the quantity of EDTA in the current drug product to 5.8 mg/dose. DGIEP has requested that the sponsor change the NDC number to reflect the new product with the lower EDTA. Our search of the ISMP Newsletters did not identify any medication errors relevant to the labels and labeling of Emend

for Injection. We find the change in the NDC number to reflect the lower amount of EDTA in the proposed Prescribing Information and carton and container labels are acceptable from a medication error perspective.

4 CONCLUSION & RECOMMENDATIONS

We find the change in the NDC number to reflect the lower amount of EDTA in the proposed Prescribing Information and carton and container labels are acceptable from a medication error perspective.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Emend for Injection that Merck and Co. submitted on August 4, 2016.

Table 2. Relevant Product Information for Emend for Injection	
Initial Approval Date	March 27, 2003
Active Ingredient	fosaprepitant dimeglumine
Indication	Indicated in adults, in combination with other antiemetic agents, for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including high-dose cisplatin and nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC)
Route of Administration	intravenous
Dosage Form	injection
Strength	150 mg
Dose and Frequency	150 mg on Day 1 as an intravenous infusion over 20 to 30 minutes approximately 30 minutes prior to chemotherapy.
How Supplied	Lyophilized powder in single-dose glass vial
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)].
Container Closure	(b) (4)

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On October 13, 2016, we searched the L: drive and AIMS using the terms, fosaprepitant, to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified two previous reviews[a,b] and we confirmed that our previous recommendations were implemented or considered.

APPENDIX C. HUMAN FACTORS STUDY – N/A

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On October 13, 2016, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care, Community, Nursing
Search Strategy and Terms	Match Exact Word or Phrase: Emend for Injection

D.2 Results

We did not identify any articles associated with medication errors or relevant to the labels and labeling for Emend for Injection.

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS) – N/A

APPENDIX F. OTHER – N/A

[a]Abraham, S. Label and Labeling Review for Emend (NDA 22023). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 11 30. 32 p. OSE RCM No.: 2015-1917.

[b]Abdus-Samad, Jibril. Label and Labeling Review for Emend (NDA 22023). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2010 08 31. 32 p. OSE RCM No.: 2009-2359.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis, along with postmarket medication error data, we reviewed the following Emend for injection labels and labeling submitted by Merck and Co. on August 4, 2016.

- Container label
- Carton labeling
- Prescribing Information

G.2 Label and Labeling Images

Proposed Container label

Proposed Carton Labeling:

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/s/

SHERLY ABRAHAM
10/31/2016

MISHALE P MISTRY
11/02/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 022023/S-014

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

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

REQUEST FOR CONSULTATION

TO *(Office/Division)*: DMEPA			FROM (*Name, Office/Division, and Phone Number of Requestor)*: Grecia C. Edward, DGIEP,OPQ	
DATE 8/28/2016	IND NO.	NDA NO. 022023/S-014	TYPE OF DOCUMENT PAS	DATE OF DOCUMENT 8/4/2016
NAME OF DRUG Emend® (Fosaprepitant Dimeglumine)	PRIORITY CONSIDERATION PAS		CLASSIFICATION OF DRUG Injection	DESIRED COMPLETION DATE 10/31/2016
NAME OF FIRM: Merck Sharp and Dohme Corp				

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☒ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS:

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check all that apply) ☒ DARRTS ☒ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

06/18/2013

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/s/

GRECIA C EDWARDS
08/28/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 022023/S-014

ACKNOWLEDGMENT --
PRIOR APPROVAL SUPPLEMENT

Merck Sharp & Dohme Corp.
a subsidiary of Merck & Co., Inc.
Attention: Nicholas W. Andrew, Director, Regulatory Affairs
1 Merck Drive, P.O. Box 100
Whitehouse Station, NJ 08889

Dear Mr. Andrew:

We have received your supplemental New Drug Application (sNDA) submitted under section 505(b)/pursuant to section 505(b) (2) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 022023

SUPPLEMENT NUMBER: 014

PRODUCT NAME: EMEND™ (fosaprepitant dimeglumine) for Injection

DATE OF SUBMISSION: August 4, 2016

DATE OF RECEIPT: August 4, 2016

This supplemental application, submitted as a "Prior Approval Supplement", provides for reduction in the concentration of EDTA, addition of a prefilter, change to analytical testing site and cap color change.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on October 3, 2016, in accordance with 21 CFR 314.101(a).

The user fee goal date will be December 4, 2016.

SUBMISSION REQUIREMENTS

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastroenterology and Inborn Error Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have questions, call Grecia C. Edwards, Regulatory Business Process Manager, at (240) 402-1773.

Sincerely,

Grecia C. Edwards, PharmD
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research